# FDA Briefing Document

# Oncologic Drugs Advisory Committee Meeting

# January 7, 2015

# BLA 125553
# EP2006, a proposed biosimilar to Neupogen® (filgrastim)
# Sandoz Inc., a Novartis company

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We bring the 351(k) BLA for EP2006 with the Applicant's proposed indications to this Advisory Committee to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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# 1 Introduction

Sandoz has submitted a biologics license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for EP 2006[1], a proposed biosimilar to Neupogen (filgrastim). Amgen's BLA # 103353 for Neupogen was initially licensed by FDA on February 20, 1991, and US-licensed Neupogen is the reference product for Sandoz' 351(k) BLA. Sandoz is seeking licensure of EP2006 for the same indications as US-licensed Neupogen:

1) to decrease the incidence of infections, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a significant incidence of severe neutropenia with fever;
2) for reducing the time to neutrophil recovery and the duration of fever, following induction or consolidation chemotherapy treatment of adults with AML[2];
3) to reduce the duration of neutropenia and neutropenia-related clinical sequelae, e.g., febrile neutropenia in patients with nonmyeloid malignancies undergoing myeloablative chemotherapy followed by marrow transplantation;
4) for the mobilization of hematopoietic progenitor cells into the peripheral blood for collection by leukapheresis; and
5) for chronic administration to reduce the incidence and duration of sequelae of neutropenia (e.g., fever, infections, oropharyngeal ulcers) in symptomatic patients with congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia.

The product is proposed to be available for use as a pre-filled syringe (PFS).

# 2 Background

### Introduction to regulatory pathway

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was passed as part of health reform (Affordable Care Act) that President Obama signed into law on March 23, 2010. The BPCI Act created an abbreviated licensure pathway for biological products shown to be "biosimilar" to or "interchangeable" with an FDA-licensed biological product (the"reference product"). This abbreviated licensure pathway under section 351(k) of the PHS Act permits reliance on certain existing scientific knowledge about the safety and effectiveness of the reference product, and enables a biosimilar biological product to be licensed based on less than a full complement of product-specific preclinical and clinical data.

[1] In this document, FDA generally refers to Sandoz' proposed product by the Sandoz descriptor "EP2006" because the Agency is continuing to consider its approach to nonproprietary naming of biosimilar biological products. Sandoz has proposed the proprietary, or brand, name of "Zarxio" for EP2006.
[2] Acute Myelogenous Leukemia

Section 351(k) of the PHS Act defines the terms “biosimilar” or “biosimilarity” to mean that “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.” A 351(k) application must contain, among other things, information demonstrating that the proposed product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies, unless FDA determines, in its discretion, that certain studies are unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act).

Development of a biosimilar product differs from development of a biological product intended for submission under section 351(a) of the PHS Act (i.e., a “stand-alone” marketing application). The goal of a “stand-alone” development program is to demonstrate the safety, purity and potency of the proposed product based on data derived from a full complement of clinical and nonclinical studies. The goal of a biosimilar development program is to demonstrate that the proposed product is biosimilar to the reference product. While both stand-alone and biosimilar product development programs generate analytical, nonclinical, and clinical data, the number and types of studies conducted will differ based on differing goals and the different statutory standards for licensure.

To support a demonstration of biosimilarity, FDA recommends that applicants use a stepwise approach to developing the data and information needed. At each step, the applicant should evaluate the extent to which there is residual uncertainty about the biosimilarity of the proposed product to the reference product and identify next steps to try to address that uncertainty. The underlying presumption of an abbreviated development program is that a molecule that is shown to be analytically and functionally highly similar to a reference product is anticipated to behave like the reference product in the clinical setting(s). The stepwise approach should start with extensive structural and functional characterization of both the proposed biosimilar product and the reference product, as this analytical characterization serves as the foundation of a biosimilar development program. Based on these results, an assessment can be made regarding the analytical similarity of the proposed biosimilar product to the reference product and the amount of residual uncertainty remaining with respect to both the structural/functional evaluation and the potential for clinically meaningful differences.

The level of residual uncertainty after the comparative analytical characterization drives both the type and amount of data needed to resolve remaining questions about whether the proposed product is “highly similar to the reference product notwithstanding minor differences in clinically inactive components” and whether there are “no clinically meaningful differences” between the proposed product and the reference product in terms of safety, purity, and potency. The results of nonclinical and/or clinical studies to resolve remaining questions should further reduce residual uncertainty and support a demonstration of biosimilarity. For example, additional data may resolve certain

questions (e.g., a structural difference with unknown impact may show no difference(s) when evaluated in appropriate functional assays) or may identify other differences (e.g., pharmacokinetic (PK) differences) that would raise concerns as well as residual uncertainty such that additional studies/data would be necessary. In both examples, while the differences may raise questions about whether the proposed biosimilar product is highly similar to the reference product, or whether there may be clinically meaningful differences between the products, identified differences should not be considered in isolation and do not necessarily preclude continued development to support a demonstration of biosimilarity. However, the applicant would need to evaluate the observed differences and explain why the differences between the proposed biosimilar product and the reference product should not preclude FDA from finding the proposed product meets the standard for biosimilarity.

The 'totality of the evidence' submitted by the applicant should be considered when evaluating whether an applicant has adequately demonstrated that a proposed product meets the statutory standard for biosimilarity to the reference product. Such evidence generally includes structural and functional characterization, animal study data, human PK and pharmacodynamics (PD) data, clinical immunogenicity data, and other clinical safety and effectiveness data.

In general, an applicant needs to provide information to demonstrate biosimilarity based on data directly comparing the proposed product with the US-licensed reference product. When an applicant's proposed biosimilar development program includes data generated using a non-US-licensed comparator to support a demonstration of biosimilarity to the US-licensed reference product, the applicant must provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and establish an acceptable bridge to the US-licensed reference product.

# 3 Executive Summary

Sandoz submitted comparative analytical data on the EP2006 lots used in clinical studies intended to support a demonstration of biosimilarity ("clinical product lots") and on the proposed commercial product. Based on our review of the data provided, Sandoz' analytical data for EP2006 demonstrates that its clinical product lots are highly similar to the reference product (US-licensed Neupogen) notwithstanding minor differences in clinically inactive components. The proposed commercial EP2006 drug product is also analytically highly similar to US-licensed Neupogen with the exception of protein content, which was slightly lower than that of US-licensed Neupogen. The lower protein content of the proposed commercial EP2006 appears to be a manufacturing issue; however, this issue may be resolved by manufacturing and control strategies.

Due to the fact that Sandoz used a non-US-licensed comparator (European Union-approved Neupogen (EU-approved Neupogen)) in some clinical studies, Sandoz was required to scientifically justify the relevance of that data to a demonstration of

biosimilarity to the US-licensed reference product. Review of the scientific justification confirms the use of these data to support a demonstration that EP2006 is biosimilar to US-licensed Neupogen.

The results of the clinical development program suggest that the Applicant's data meets the requirement for a demonstration of "no clinically meaningful differences" between the proposed product and the reference product in terms of safety, purity, and potency. Specifically, the results from the comparative PK and PD studies in normal human healthy subjects (i.e., PK and PD similarity studies), which were extensive and robust both in terms of the number of the studies and the number of different SC doses of EP2006 (1.0, 2.5, 5.0 and 10 mcg/kg), EU-approved Neupogen (1, 2.5, 5 and 10 mcg/kg), and US-licensed Neupogen (5 and 10 mcg/kg), adequately supported that there are no clinically meaningful differences between EP2006 and US-licensed Neupogen.

This conclusion was also supported by a comparative clinical study, EP06-302, which enrolled patients with breast cancer receiving TAC chemotherapy who were randomized to receive either EP2006 or US-licensed Neupogen. FDA's analysis of the efficacy and safety results of EP06-302 focused on Cycle 1 and these data provided additional support that there are no clinically meaningful differences between EP2006 and US-licensed Neupogen.

The issues identified with the protein content of the EP2006 proposed commercial lots do not affect this conclusion because the clinical trials utilized the clinical product lots of EP2006.

At the time of the completion of this briefing document additional data on the comparative immunogenicity analysis of EP2006 and US-licensed Neupogen are pending and may be forthcoming before the ODAC meeting on January 7, 2015.

# 4 Draft Questions to the Committee

Questions to the committee:

1. Does the committee agree that, based on the data presented, EP2006 is highly similar to the reference product (US-licensed Neupogen), notwithstanding minor differences in clinically inactive components?

2. Does the committee agree that based on the totality of the evidence, the clinical product lots of EP2006 are biosimilar to US-licensed Neupogen?

3. Does the committee agree that the data show that there are no clinically meaningful differences between EP2006 and US-licensed Neupogen in terms of safety and effectiveness?

4. Does the committee agree that based on the totality of the evidence, EP2006 should receive licensure for each of the 5 indications for which US-licensed Neupogen is currently licensed?

# 5 CMC

**Executive summary**

EP2006 is a proposed biosimilar to US-licensed Neupogen. Analytical similarity of EP2006 to US-licensed Neupogen was evaluated using methods to assess physicochemical and functional properties of the products. Comparison of product-related substances and impurities and comparative stability studies were also conducted. The analytical similarity results indicate that EP2006 is highly similar to the reference product, US-licensed Neupogen.

EP2006 also has been evaluated in various clinical studies. Some of these studies used a non-US-licensed comparator product (European Union-approved Neupogen (EU-approved Neupogen)). To justify the use of these comparative clinical data to support a demonstration of biosimilarity of EP2006 to US-licensed Neupogen, the Applicant needed to establish an adequate scientific bridge. The Applicant conducted analytical pair-wise comparisons of EP2006, US-licensed Neupogen, and EU-approved Neupogen to establish an analytical bridge. The results of these comparisons show that the three products meet the pre-specified criteria for analytical similarity. Thus, an adequate analytical bridge between the three products was established.

**Mechanism of action of Granulocyte Colony Stimulating Factor (G-CSF)**

The reference product, US-licensed Neupogen, contains recombinant methionyl Granulocyte Colony Stimulating Factor (met-G-CSF). The approved indications of US-licensed Neupogen generally fall under the categories of neutropenia and mobilization of hematopoietic stem cells.

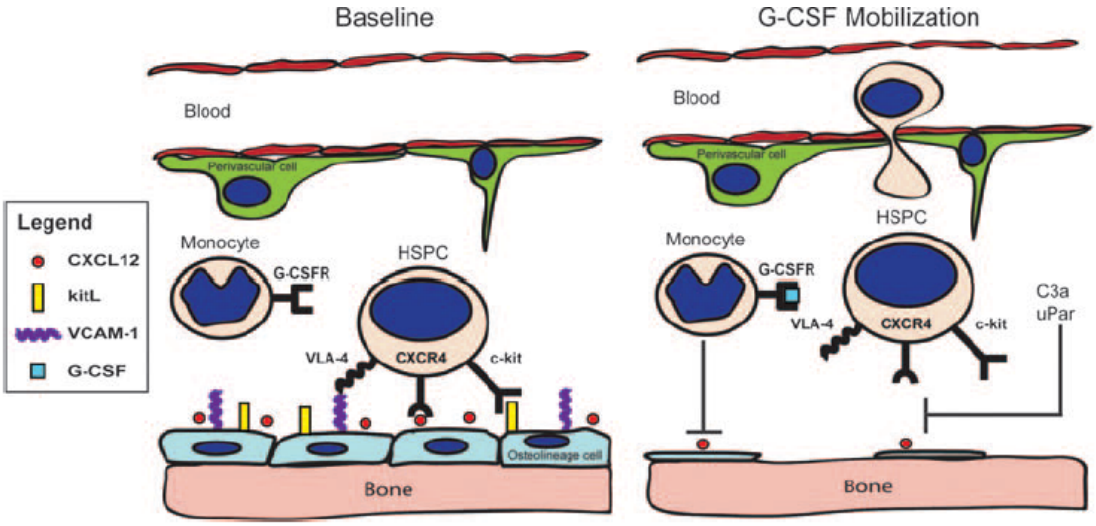
The biological activity of G-CSF is initiated by binding of G-CSF to the G-CSF receptor on myeloid progenitor cells and mature neutrophils. This binding initiates transduction signals that lead to the proliferation and differentiation of neutrophil committed progenitor cells, increase of mature neutrophils in the blood (which is an acceptable pharmacodynamic marker for neutropenia), and enhanced neutrophil function[1]. These functions are all relevant to the neutropenia indications.

The mechanism of action related to the mobilization of hematopoietic stem cells indication is not fully understood. However, reports in the literature strongly suggest that

1. Panopoulus, A.D. and Watowich, S.S. (2008). Granulocyte colony-stimulating factor: Molecular mechanisms of action during steady state and 'emergency' hematopoiesis. Cytokine 42: 277-288

the G-CSF receptor plays critical role in the mobilization of hematopoietic stem cells (HSC)[2]. A model of G-CSF-induced mobilization is presented in Figure 1[2]. In this representation, mobilization of HSC is initiated by binding of G-CSF to the G-CSF receptor on monocytic cells in the bone marrow. This leads to changes in cells of the osteoblast lineage which results in the disruption of key interactions that regulate HSC. The absence of key interactions between cells of the osteoblast lineage and HSC result in mobilization of HSC into the blood stream. Hematopoietic stem cells are identified by the presence of the cluster differentiation protein 34 (CD 34) marker on their surface (which is an acceptable pharmacodynamic marker for stem cell mobilization)[3].

**Figure 1. Model of G-CSF-induced HSPC mobilization[2]**




Model of G-CSF-induced HSPC mobilization. At baseline (left panel), osteoblast lineage cells produce key molecules such as CXCL12, VLA-4 and c-kit that retain HSPCs in the bone marrow. G-CSF signaling in monocytic cells results in the production (or suppression) of currently undefined transacting signals that, in turn, result in the suppression of osteoblast lineage cells (right panel). The net effect of this signaling cascade is the disruption of key interactions that regulate HSPC function, most notably CXCL4/CXCL12 signaling. Mobilization is also augmented by other pathways which alter CXCR4 signaling, such as complement and uPAR activation.

## EP2006 manufacturing

EP2006 (met-G-CSF) is produced by recombinant technology in *Escherichia coli* (*E. coli*). The manufacturing process of EP2006 drug substance consists of various steps intended to isolate and purify met-C-GSF. Process-related impurities such as host (*E. coli*) cell proteins (HCP), host cell DNA (HCDNA) as well as other process-related

2. Greenbaum AM and Link DC (2011). Mechanisms of G-CSF-mediated hematopoietic stem and progenitor mobilization. Leukemia, 25: 211-217
3. Aiuti A, et al. (1997). The Chemokine SDF-1 Is a Chemoattractant for Human CD34+ Hematopoietic Progenitor Cells and Provides a New Mechanism to Explain the Mobilization of CD34+ Progenitors to Peripheral Blood J Exp Med, 185: 111–12

impurities specific to the EP2006 process were evaluated in EP2006 drug substance. Data were provided to demonstrate that the manufacturing process of EP2006 drug substance is able to reduce the levels of these impurities to very low levels (e.g., ppm for HCP and pg/mg EP2006 protein for HCDNA).

Bacterial endotoxins were evaluated in both EP2006 drug substance and drug product and are in agreement with bacterial endotoxins compendial requirements.

EP2006 drug product was developed as a liquid, injection, filled in a pre-filled syringe (PFS) in the same strengths (300 mcg/0.5 ml and 480 mcg/0.8 ml) and for the same indications as those approved for US-licensed Neupogen[4]. The formulation of EP2006 differs from the formulation of US-licensed Neupogen in an inactive ingredient and pH. US-licensed Neupogen's formulation includes acetate[4] whereas EP2006's formulation includes glutamate.

The manufacturing process of EP2006 drug substance and drug product changed during the clinical development program. Sandoz provided data to demonstrate that the EP2006 drug substance manufactured by the proposed commercial process (referred to as proposed commercial product) is comparable to the drug substance used to manufacture the EP2006 drug product used in the clinical studies (referred to as clinical product). With the exception of protein content (discussed below in the analytical similarity section), the drug product manufactured by the proposed commercial process is comparable to the drug product manufactured by the clinical process.

The EP2006 drug substance and drug product processes are validated and produce product of consistent quality. The controls of the EP2006 drug substance and drug product meet regulatory requirements and the initial assessment of the manufacturing facilities indicate that they are acceptable from a good manufacturing practice (GMP) perspective.

**Studies to support biosimilarity**

Five PK and PD (EP06-101, EP06-102, EP06-103, EP06-105 and EP06-109) and two efficacy (EP06-301 and EP06-302) studies have been conducted with EP2006 since 2004. Studies EP06-101, EP06-102, EP06-103, EP06-301 and EP06-105 compare EP2006 with EU-approved Neupogen. Studies EP06-109 and EP06-302 compare EP2006 with US-licensed Neupogen. Given that certain clinical studies intended to support a demonstration that EP2006 is biosimilar to US-licensed Neupogen were conducted with a non-US-licensed comparator (EU-approved Neupogen), an adequate scientific bridge between EP2006, US-licensed Neupogen and EU-approved Neupogen needed to be established.

4. US-licensed Neupogen labeling approved on September 13, 2013, at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/103353s5157lbl.pdf, retrieved November 11, 2014.

**Analytical similarity**

The analytical similarity data discussed in this section were provided by Sandoz and correspond to Sandoz' analysis of the products under evaluation.

Analytical similarity of EP2006, US-licensed Neupogen, and EU-approved Neupogen was assessed by evaluating batches of each of the three products. A total of 17 batches of EP2006 drug product (DP), 6 batches of EP2006 drug substance (DS), 10-15 batches of US-licensed Neupogen and 34-52 batches of EU-approved Neupogen were evaluated. The number of batches analyzed was justified by the Applicant and based on the variability of the analytical method and availability of material. The EP2006 DP batches analyzed included batches used in clinical studies EP06-101, EP06-102, EP06-103 and EP06-301 and in non-clinical studies EP06-004 and EP06-006 (the process used to manufacture these batches is referred to as "clinical process"). Batches of EP2006 DP manufactured by the proposed commercial process were also analyzed and are referred to in this document as "commercial process."

Based on the labeled expiration dates, the US-licensed Neupogen and EU-approved Neupogen batches analyzed span approximately 5 years and 10 years, respectively. The EP2006 batches analyzed were manufactured between 06/2004 and 11/2005 (clinical batches) and 07-08/2011 (commercial batches). Analytical testing was conducted 25-27 months before expiry of the EP2006 batches and 2-20 months before expiry of the US-licensed Neupogen and EU-approved Neupogen.

The analytical comparison of EP2006 and US-licensed Neupogen is used to support a demonstration that EP2006 is "highly similar to the reference product [US-licensed Neupogen] notwithstanding minor differences in clinically inactive components." Pair-wise comparisons of EP2006, US-licensed Neupogen, and EU-approved Neupogen are used to support an analytical bridge between the three products. This bridge is needed to demonstrate that all three products meet the pre-specified criteria for analytical similarity and to justify the relevance of the comparative data generated using EU-approved Neupogen from some clinical and non-clinical studies.

Analytical similarity of EP2006, US-licensed Neupogen and EU-approved Neupogen was assessed using the methods listed in Table 1. The methods were validated or qualified at the time of testing and demonstrated to be fit for intended use.

**Table 1: Quality attributes and methods used to evaluate analytical similarity of EP2006, US-licensed Neupogen and EU-approved Neupogen**

| Quality Attribute | Methods |
|---|---|
| Primary structure | • N-terminal sequencing<br>• Peptide mapping with ultraviolet (UV) and mass spectrometry detection<br>• Protein molecular mass by electrospray mass |

| Quality Attribute | Methods |
|---|---|
| | spectrometry (ESI MS)<br>• Protein molecular mass by matrix-assisted laser desorption ionization mass spectrometry (MALDI-TOF MS)<br>• DNA sequencing of the EP2006 construct cassette<br>• Peptide mapping coupled with tandem mass spectrometry (MS/MS) |
| Bioactivity | • Proliferation of murine myelogenous leukemia cells (NFS-60 cell line) |
| Receptor binding | • Surface Plasmon Resonance |
| Protein content | • RP-HPLC |
| Higher order structure | • Far and Near UV circular dichroism<br>• Proton ($^{1}H$) nuclear magnetic resonance<br>• Proton-Nitrogen ($^{1}H$-$^{15}N$) heteronuclear single quantum coherence spectroscopy<br>• Liquid chromatography coupled with mass spectrometry (LC-MS) (disulfide bond characterization) |
| Clarity | • Nephelometry |
| Sub-visible particles | • Micro flow imaging |
| High molecular weight species/aggregates | • Size exclusion chromatography<br>• Reduced and non-reduced sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) |
| Oxidized species | • Reverse Phase High Performance Liquid chromatography (RP-HPLC)<br>• Liquid chromatography coupled with mass spectrometry (LC-MS) |
| Covalent dimers | • Liquid chromatography coupled with mass spectrometry (LC-MS) |
| Partially reduced species | • Liquid chromatography coupled with mass spectrometry (LC-MS) |
| Sequence variants:<br>His→Gln<br>Asp→Glu<br>Thr→Asp | • Liquid chromatography coupled with mass spectrometry (LC-MS) |
| fMet1 species | • Liquid chromatography coupled with mass spectrometry (LC-MS) |
| Succinimide species | • Liquid chromatography coupled with mass spectrometry (LC-MS) |
| Phosphoglucunoylation | • Liquid chromatography coupled with mass spectrometry (LC-MS) |
| Acetylated species | • Liquid chromatography coupled with mass spectrometry (LC-MS) |
| N-terminal truncated species | • Liquid chromatography and tandem mass |

| Quality Attribute | Methods |
|---|---|
| | spectrometry (LC-MS/MS) |
| Norleucine species | • Liquid chromatography coupled with mass spectrometry (LC-MS) |
| Deamidation species | • Reverse Phase High Performance Liquid chromatography (RP-HPLC)<br>• Liquid chromatography coupled with mass spectrometry (LC-MS)<br>• Isoelectric focusing<br>• Cation exchange chromatography |

**Primary structure**

The primary structure (amino acid sequence) of the three products was determined using the methods listed in Table 1.

N-terminal sequencing results indicate that the first seven amino acids of EP2006 (i.e., MTPLGPA) are the same first seven amino acids of the US-licensed Neupogen and EU-approved Neupogen. These seven amino acids are identical to the amino acids deduced from the EP2006 plasmid DNA sequence bearing the met-G-CSF gene and they are also identical to the sequence of purified met-G-CSF reported in the literature[5].

The Applicant demonstrated that the peptide map data of EP2006 has a similar chromatographic profile (map) as US-licensed Neupogen and EU-approved Neupogen (e.g., Figure 2). No additional peptides or missing peptides were detected between the three products. In addition, the experimentally determined peptide masses determined by mass spectrometry (data not shown) of EP2006 are all consistent with the Applicant's evaluation of US-licensed Neupogen and EU-approved Neupogen and with the theoretical peptide masses deduced from the met-G-CSF sequence reported in the literature[5]. Mass spectrometry analysis also confirms the presence of two disulfide bonds at Cys37-Cys43 and Cys65-Cys75 in the three products.

5. Herman AC, et.al. (1996). Characterization, formulation, and stability of Neupogen (Filgrastim), a recombinant human granulocyte-colony stimulating factor. Pharm Biotechnol; 9, 303-328

**Figure 2. UV chromatograms of RP-HPLC of Glu-C digested Filgrastim from EP2006 drug product and US-licensed Neupogen 480 mcg/0.8 mL and EU-approved Neupogen 480 mcg/0.5 mL* drug product batches**

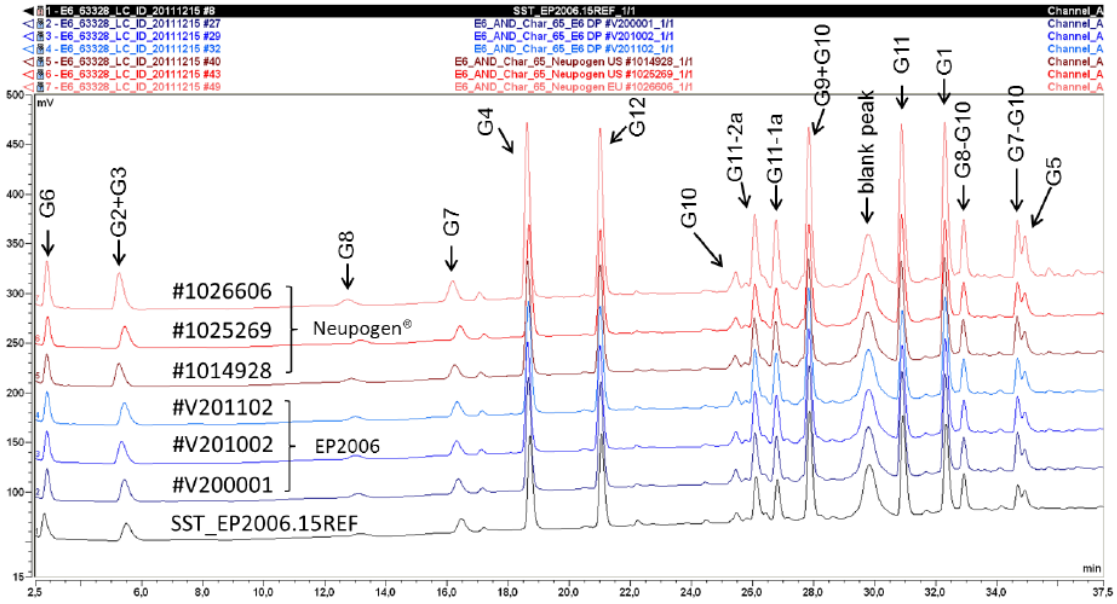



*Figure excerpted from Sandoz 351(k) BLA submission*
** EU-approved Neupogen is approved in a different concentration (480 mcg/0.5 ml) than that of US-licensed Neupogen (480 mcg/0.8 ml)*

The mass of the intact met-G-CSF protein determined by mass spectrometry (ESI MS and MALDI MS) was highly similar in the three products and in agreement with the theoretical mass of met-G-CSF. These results further support the primary sequence of the three products.

The DNA sequence of the expression cassette of EP2006 indicates that this producing plasmid encodes the human G-CSF gene[6] with an additional methionine at the N-terminus. Restriction analysis of the expression plasmid extracted from the producing strain cultured at and beyond the regular production period is of the expected pattern based on the DNA sequence and specificity of the restriction enzymes used. The primary sequence of EP2006 deduced by amino acid analysis, tandem mass spectrometry (MS/MS) of peptides derived from treatment with three proteases (Glu-C, pepsin and chymortrypsin) and N-terminal sequencing of Glu-C digested peptides indicate that the sequence of EP2006 is identical to that of the met-G-CSF protein reported in the literature[5].

Taken together, these data provide strong evidence that the sequences of EP2006, US-licensed Neupogen, and EU-approved Neupogen are the same.

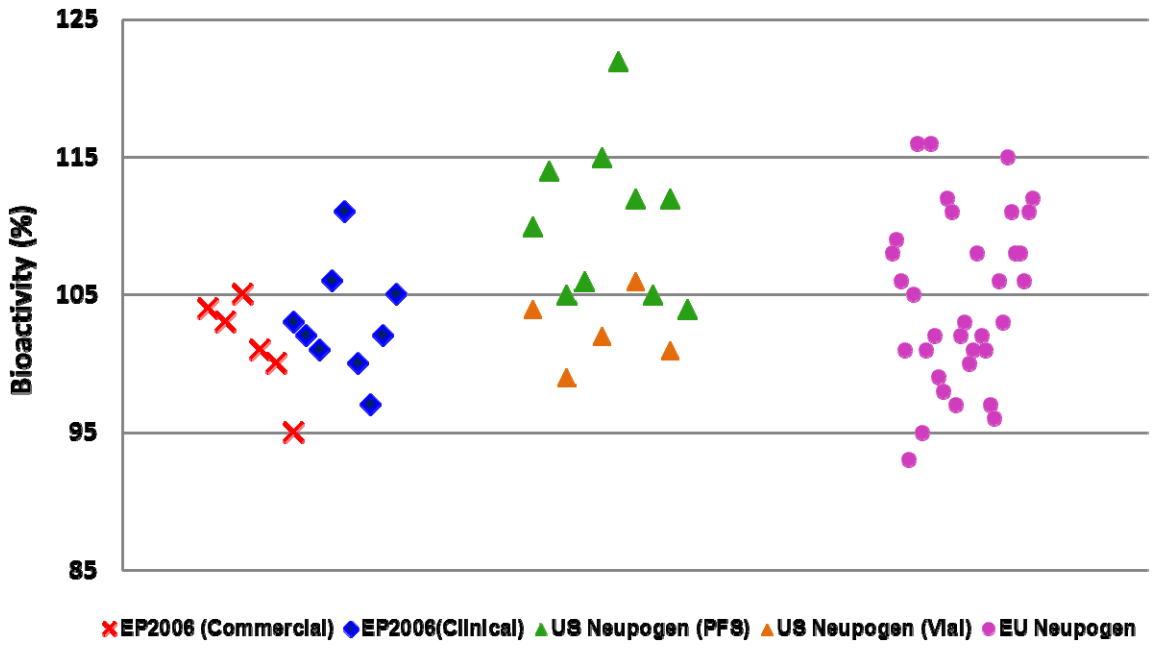
6. http://www.uniprot.org/uniprot/P09919

**Biological activity**

A cell proliferation assay using murine myelogenous leukemia cells (NFS-60 cell line) was used to evaluate the biological activity of the three products. This cell line carries the G-CSF receptor and it is commonly used to evaluate the biological activity of this growth factor[7].

The bioactivity data were reported as percentage relative to the applicant's in-house reference standard calibrated against an international G-CSF reference standard (Figure 3). These data were subjected to a statistical analysis using equivalence testing. Statistical equivalence is considered to be met if the 90% confidence interval (CI) of the mean difference between EP2006 and US-licensed Neupogen is entirely within an equivalence acceptance criterion calculated from the Applicant's data on US-licensed Neupogen. Descriptive statistics for biological activity are summarized in Table 2.

**Figure 3. Biological activity of EP2006, US-licensed Neupogen and EU-approved Neupogen**




7. Shirafuji, N. et. al. A new bioassay for human granulocyte colony-stimulating factor (hG-CSF) using murine myeloblastic NFS-60 cells as targets and estimation of its levels in sera from normal healthy persons and patients with infectious and hematological disorders. Experimental Hematology (1989). 17: 116-9

The batches of US-licensed Neupogen evaluated span approximately 5 years whereas the batches of EU-approved Neupogen span approximately 10 years.

**Table 2: Descriptive Statistics for Bioactivity (%)**

| Product | # batches | Min | Max | Mean | Standard Deviation | CV [a](%) |
|---|---|---|---|---|---|---|
| EP2006 (clinical and commercial, PFS) | 15 | 95 | 111 | 102.3 | 3.81 | 3.72% |
| US-Neupogen (PFS and Vial) | 15 | 99 | 122 | 107.8 | 6.21 | 5.76% |
| EU-Neupogen (PFS) | 34 | 93 | 116 | 104.7 | 6.18 | 5.91% |

[a] CV: coefficient of variability

In the statistical analysis, bioactivity data from batches of US-licensed Neupogen in the PFS and vial presentations were included because both presentations represent the profile of the reference product patients receive. Among other things, US-licensed Neupogen in vials and in PFS are used for the same indications and are administered by the same routes of administration[4]. In addition, the applicant provided data demonstrating that both US-licensed Neupogen presentations, PFS and vial are analytically similar.

The statistical analysis results indicate statistical equivalence of the biological activity of the three products (Table 3). This assessment supports that the biological activity of EP2006 and US-licensed Neupogen is highly similar. The statistical evaluation also contributes to supporting an analytical bridge between the three products.

**Table 3. Equivalence testing of bioactivity data**

| Product* | # batches | Comparator Product | # batches | Statistical Equivalence? |
|---|---|---|---|---|
| EP2006 (clinical and commercial batches) | 15 | US-Neupogen (PFS and vials) | 15 | **Yes[a]** |
| EP2006 (clinical and commercial batches) | 15 | EU-Neupogen (PFS) | 15 | **Yes[b]** |
| EU-Neupogen | 34 | US-Neupogen (PFS and vials) | 15 | **Yes[c]** |

* All PFS

[a] The 90% confidence interval (CI) of the mean difference between EP2006 and US-licensed Neupogen (-8.67%, -2.27%) is entirely within the equivalence acceptance criterion of (-9.32%, 9.32%)

[b] The 90% CI of the mean difference between EP2006 and EU-approved Neupogen (-5.47%, 0.54%) is entirely within the equivalence acceptance criterion of (-10.07%, 10.07%)

[c] The 90% CI of the mean difference between EU-approved Neupogen and US-licensed Neupogen (-6.34%, 0.10%) is entirely within the equivalence acceptance criterion of (-9.32%, 9.32%)

## Receptor binding

Binding of the met-G-CSF to the G-CSF receptor was investigated by surface plasmon resonance (SPR). Representative binding curves are presented in Figure 4. The binding parameters calculated from these experiments include receptor association rate (Kon), dissociation rate (koff) and equilibrium dissociation rate (KD) constants. Using the Applicant's data on US-licensed Neupogen, a similarity range defined as the mean ± 2 standard deviations (SD) was calculated. Individual binding parameters of EP2006 and EU-approved Neupogen were then compared to this range. With few exceptions, the binding parameters determined for EP2006 and EU-approved Neupogen are within the reference product (US-licensed Neupogen) range. It is important to mention that some exceptions are expected due to assay variability between experiments. Taking all these data together, the binding parameters of the three products are considered highly similar.

**Figure 4. Binding curves of EP2006, US-licensed Neupogen and EU-approved Neupogen**

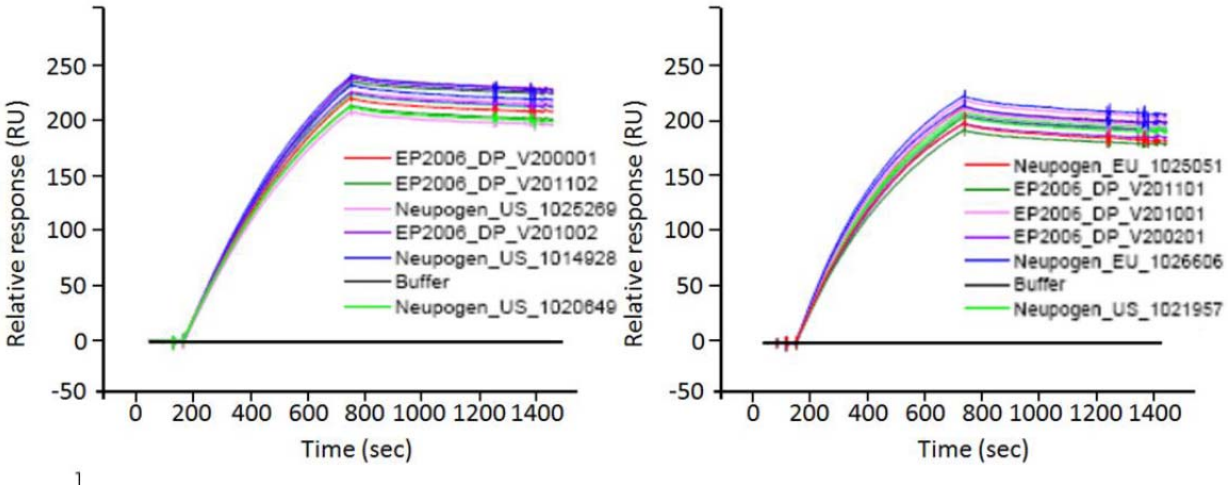



*Figure excerpted from Sandoz 351(k) BLA submission*

As summarized in the first section of this document, the mechanism of action of G-CSF related to the neutropenia and mobilization HSC indications requires binding of G-CSF to the G-CSF receptor. The results summarized above show that binding of EP2006 and US-licensed Neupogen to the G-CSF receptor is highly similar. The results of the cell-based bioassay, which also requires binding of the products to the G-CSF receptor on NSF-60 cells and subsequent signaling pathways that leads to their proliferation, are

also highly similar. Based on these results, it is concluded that EP2006 and US-licensed Neupogen have the same mechanism of action for each of the conditions of use for which licensure is sought. This is further supported by a demonstration that both products have the same primary structure, corresponding to met-G-CSF and have highly similar secondary and tertiary structure (see below).

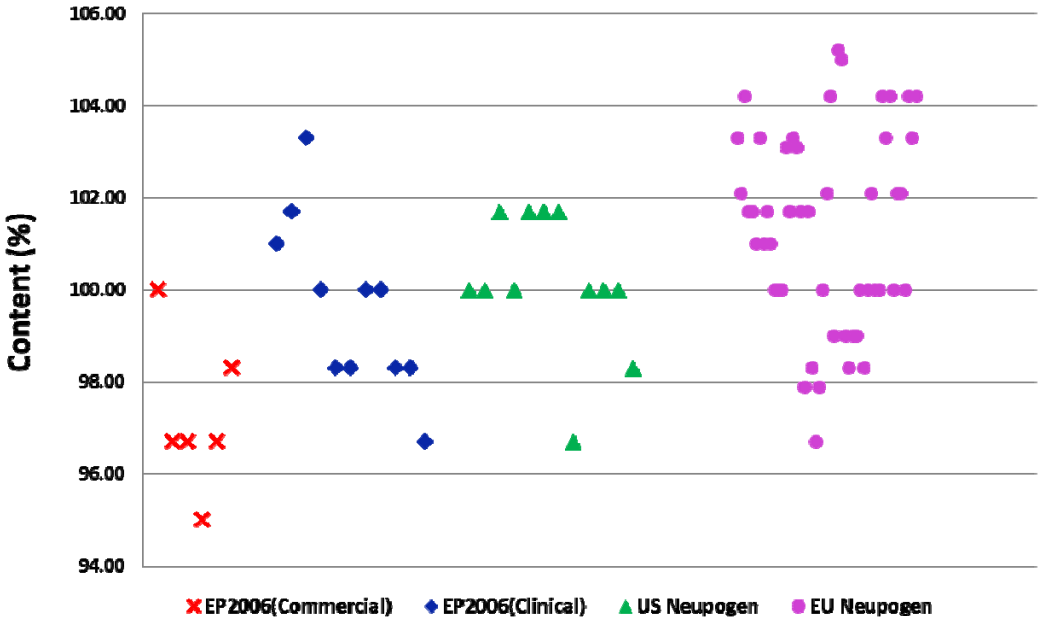
### Protein concentration (content by RP-HPLC)

The concentration of met-G-CSF (μg/ml) in EP2006, US-licensed Neupogen and EU-approved Neupogen was determined by RP-HPLC. Content data of drug product manufactured by the clinical and commercial processes were provided. Descriptive statistics and graphical representation of the historical data, expressed as percentage of the declared content are shown Table 4 and Figure 5.

**Table 4: Descriptive Statistics for Content (%)**

| Product | # of Batches | Min | Max | Mean | Standard Deviation | CV(%) |
|---|---|---|---|---|---|---|
| US-Neupogen | 12 | 96.7 | 101.7 | 100.15 | 1.51 | 1.51% |
| EU-Neupogen | 49 | 96.7 | 105.2 | 101.33 | 2.14 | 2.11% |
| Clinical EP2006 | 11 | 96.7 | 103.3 | 99.63 | 1.89 | 1.90% |
| Commercial EP2006 | 6 | 95.0 | 100.0 | 97.23 | 1.71 | 1.76% |

**Figure 5. Content results of EP2006, US-licensed Neupogen and EU-approved Neupogen**



The batches of US-licensed Neupogen evaluated span approximately 5 years whereas the batches of EU-approved Neupogen span approximately 10 years.

As can be seen in Table 4 and Figure 5, content of EP2006 batches manufactured by the clinical process (mean 99.63%) is highly similar to US-licensed Neupogen (100.15%) and EU-approved Neupogen (101.33%). However, content of EP2006 batches manufactured by the commercial process (mean 97.23%) is 2.92% lower (mean differences) than that of US-licensed Neupogen. To resolve this uncertainty, statistical equivalence testing was conducted on these data. The results are shown in Table 5.

**Table 5. Equivalence Testing Results for Content**

| Product | # batches | Comparator product | # batches | Statistical Equivalence? |
|---|---|---|---|---|
| EP2006 (Clinical) | 11 | US-Neupogen | 12 | **Yes**[a] |
| EP2006 (Commercial) | 6 | US-Neupogen | 12 | **No**[b] |
| EP2006 (Clinical) | 11 | EU-Neupogen | 11 | **Yes**[c] |
| EU-Neupogen | 49 | US-Neupogen | 12 | **Yes**[d] |

[a] The 90% confidence interval (CI) of the mean difference between clinical EP2006 and US-licensed Neupogen (-1.75%, 0.70%) is entirely within the equivalence acceptance criterion of (-2.26%, 2.26%)

[b] The 81.4% CI of the mean difference between commercial EP2006 commercial and US-licensed Neupogen (-3.87%, -1.13%) is not completely entirely within the equivalence acceptance criterion of (-2.08%, 2.08%)

[c] The 90% CI of the mean difference between clinical EP2006 and EU-approved Neupogen (-2.32%, 0.52%) is entirely within the equivalence acceptance criterion of (-3.23%, 3.23%)

[d] The 90% confidence interval of the mean difference between EU-approved Neupogen and US-licensed Neupogen (0.27%, 2.09%) is entirely within the equivalence acceptance criterion of (-2.26%, 2. 26%).

The statistical evaluation confirmed that the protein content of EP2006 manufactured by the clinical process is highly similar to the protein content in US-licensed Neupogen and EU-approved Neupogen. However, the 6 batches of EP2006 manufactured by the commercial process are lower in protein content than the comparator products and do not meet statistical equivalence.

The lower content of commercial EP2006 appears to be a manufacturing issue. However, this issue can likely be resolved by manufacturing and control strategies.

Sandoz was asked to address this deficiency and provide data demonstrating that the proposed commercial EP2006 has the same "strength"[8] as US-licensed Neupogen.

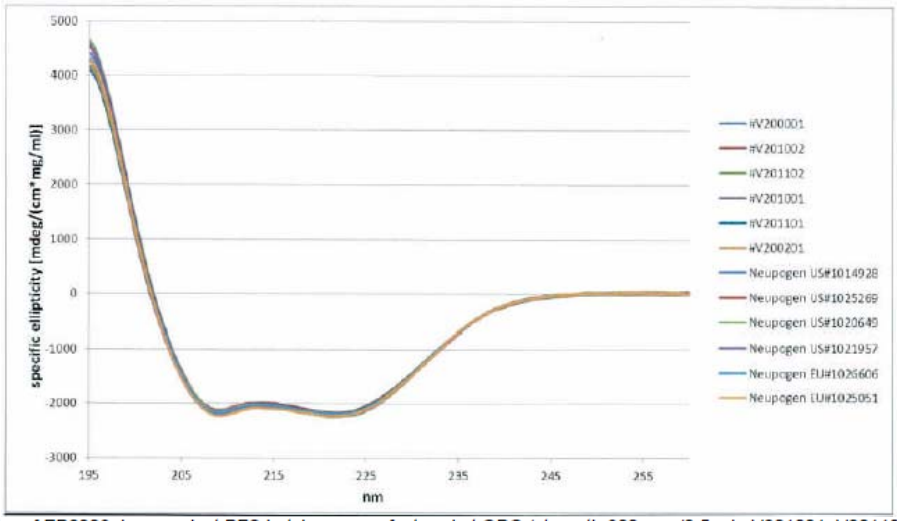
As indicated above, EP2006 manufactured by the clinical process is highly similar to US-licensed Neupogen and EU-approved Neupogen. Thus, the clinical data generated with this product may be used to support a demonstration of biosimilarity.

**Higher order structure (HOS)**

Secondary and tertiary structures of the products were evaluated by far and near UV circular dichroism, and 1D and 2D nuclear magnetic resonance (Table 1).

Far and near UV CD spectroscopy provides information about secondary ($\alpha$-helix, $\beta$-sheet and random coil structures) and tertiary structure, respectively. Representative far and near UV CD spectra for EP2006, US-Licensed Neupogen and EU-approved Neupogen are shown in Figures 6 and 7.

**Figure 6. Far UV CD spectra of EP2006 DP and [US-licensed Neupogen and EU-approved Neupogen] batches**




Overlay of CD spectra of EP2006 drug product PFS batches, manufactured at GPG (strength 300 mcg/0.5 mL: V201001, V201101, V200201; strength 480 mcg/0.8 mL: V200001, V201002, V201102), US licensed Neupogen® US PFS batches (strength 300 mcg/0.5 mL: 1020649, 1021957; strength 480 mcg/0.8 mL: 1014928, 1025269), and non-US licensed Neuogen® EU PFS batches (strength 300 mcg/0.5 mL: 1025051; strength 480 mcg/0.8 mL: 1026606).

*Figure excerpted from Sandoz 351(k) BLA submission*

8. Section 351(K)(2)(A)(i)(IV) of the PHS Act

**Figure 7. Near UV CD spectra of EU-approved Neupogen (red) and EP2006 (black) active ingredient at various PH values**

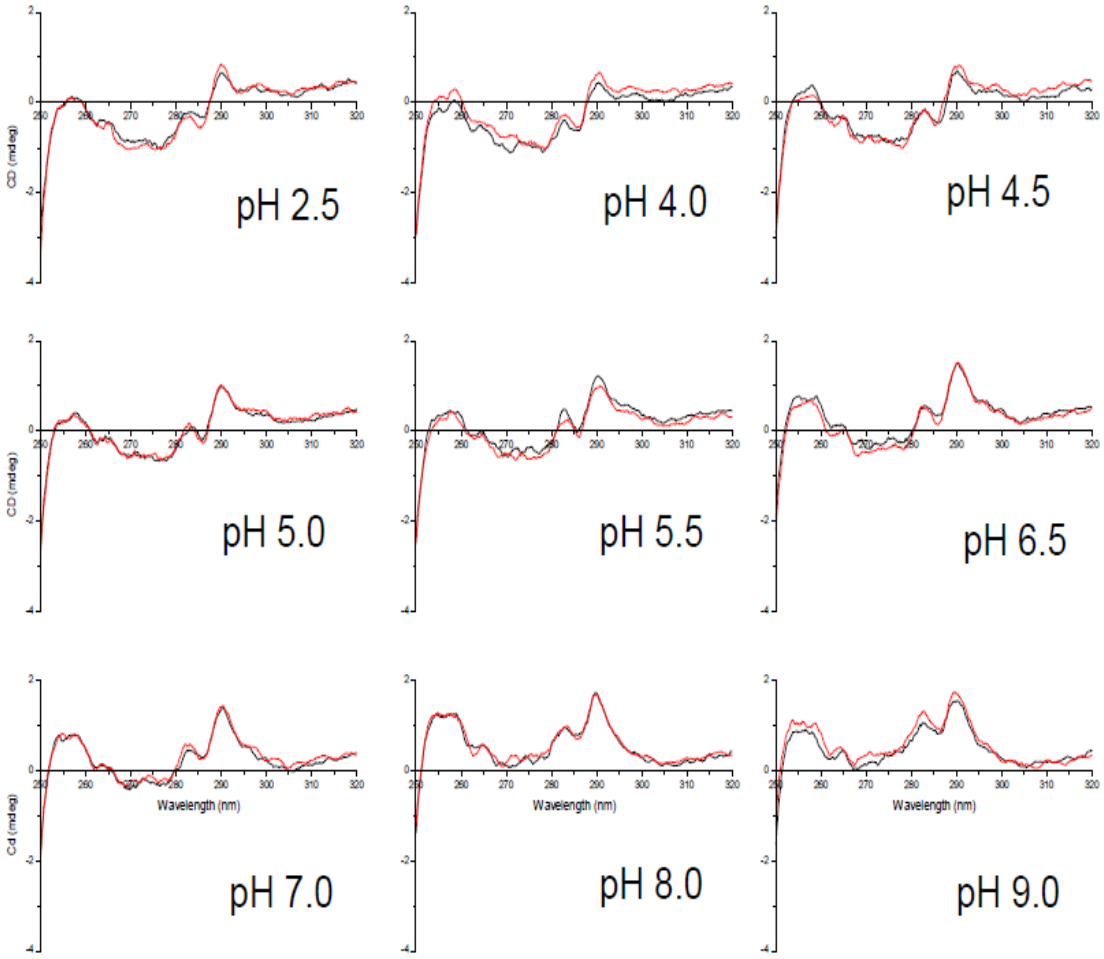


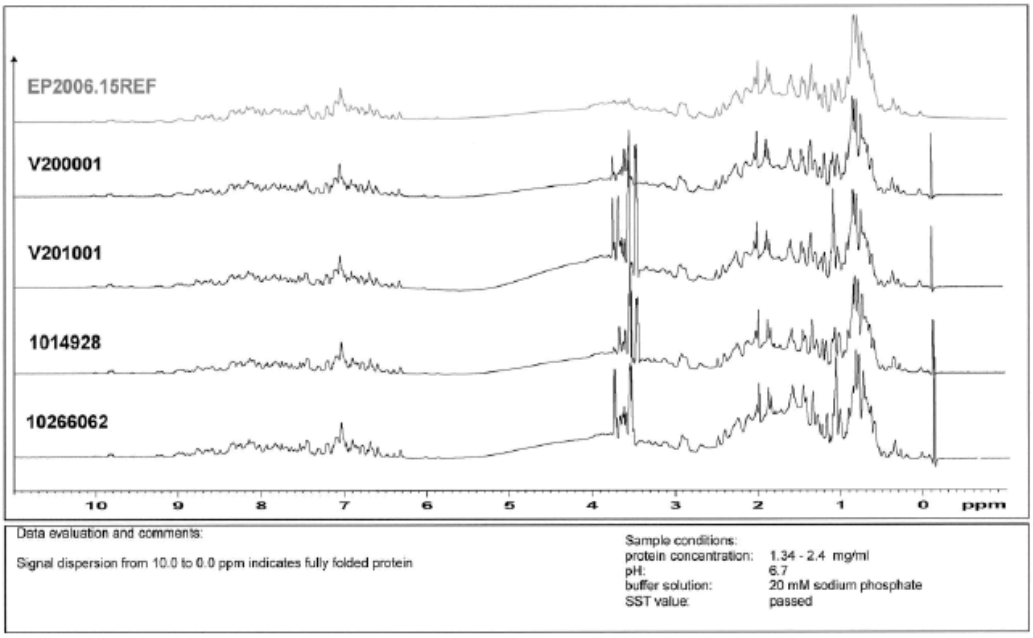

*Figure excerpted from Sandoz 351(k) BLA submission*

In addition to similar CD spectra, comparison of transition point (specific ellipticity = 0) and ratio of specific ellipticity ($\theta_{R208}/\theta_{R222}$) data derived from the far UV CD spectra contribute to showing that the three products are highly similar.

$^{1}$H NMR spectroscopy provides information about the three dimensional structure of the protein. Presence of spread proton signals in the amide region (8.5 ± 3 ppm) is indicative of a protein in folded state. Representative spectra of EP2006, US-licensed Neupogen and EU-approved Neupogen are provided below. No significant difference in

the spectra of EP2006 compared to US-licensed Neupogen and EU-approved Neupogen were detected.

**Figure 8. Superposition of full NMR spectra of selected batches (study 1)**




Superposition of full NMR spectra of selected batches (study 1): EP2006.15REF reference standard, EP2006 DP 480 mcg/0.8 mL and 300 mcg/0.5 mL from GPG (V200001, V201001), Neupogen® US 480 mcg/0.8 mL (1014928) and EU 480 mcg/0.5 mL (1026606) material are shown

*Figure excerpted from Sandoz 351(k) BLA submission*

To further support higher order structure (HOS) similarity, natural isotope abundance 2D NMR ($^{1}H$-$^{15}N$ HSQC) spectra of the three products were also recorded. Assignment of $^{1}H$-$^{15}N$ NMR signals has been reported previously.[9] The signals in the $^{1}H$-$^{15}N$ HSQC spectrum correspond to N-H pairs (primarily peptide amide groups) of met-G-CSF.

$^{1}H$-$^{15}N$ NMR provides better resolution than $^{1}H$ NMR and may be considered a structural fingerprint of the protein. $^{1}H$-$^{15}N$ HSQC spectra of EP2006 DP, US-licensed Neupogen, and EU-approved Neupogen were recorded in the US-licensed Neupogen formulation (acetates, pH 4.0) and in the EP2006 formulation (glutamates pH 4.4.) Overlays of the spectra are shown in Figures 9 and 10. Each signal of EP2006, which generally correspond to each residue of the protein, overlap with the signals of US-licensed Neupogen and EU-approved Neupogen.

9. Zink, T. et al (1994). Structure ad Dynamics of the Human Granulocyte Colony Stimulating Factor Determined by NMR Spectroscopy. Loop mobility in a four-Helix-Bundle Protein. Biochemistry 33, 8453-8463 and http://www.bmrb.wisc.edu/data_library/summary/index.php?bmrbId=18291.

In addition, 2D spectra of EP2006 in different pH values (3.0, 4.0 and 4.4) were recorded to demonstrate that the method is able to identify changes in chemical shift of the N-H signals due to different environment.

**Figure 9. Overlay of EP2006 batch V201002 (cyan), [US-licensed Neupogen] (orange) and [EU-approved Neupogen] (green) $^{1}H$-$^{15}N$ HSQC spectra in the US-licensed Neupogen formulation**

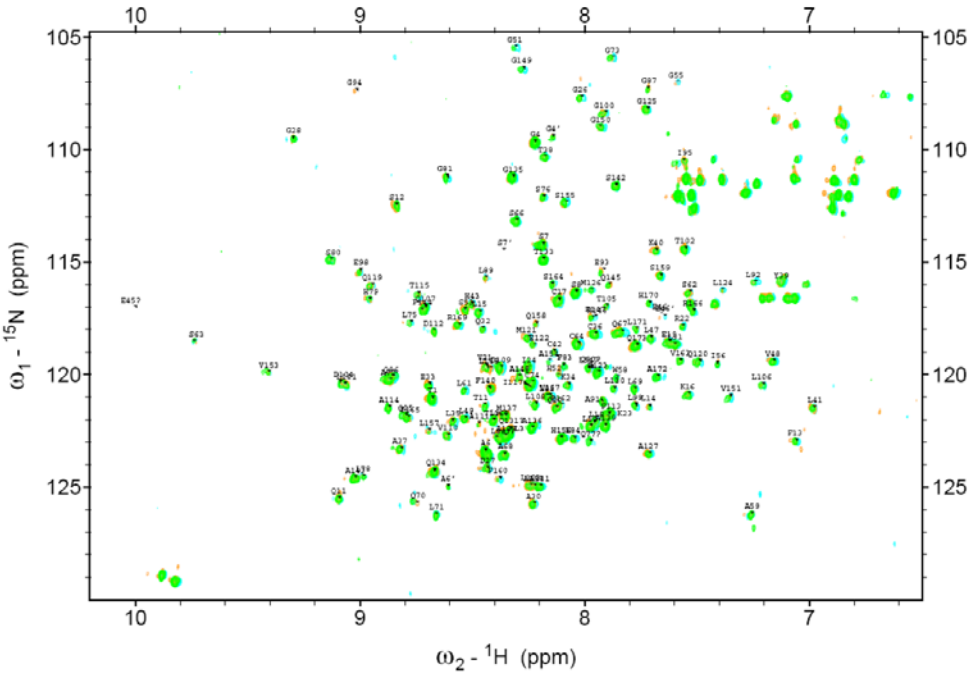
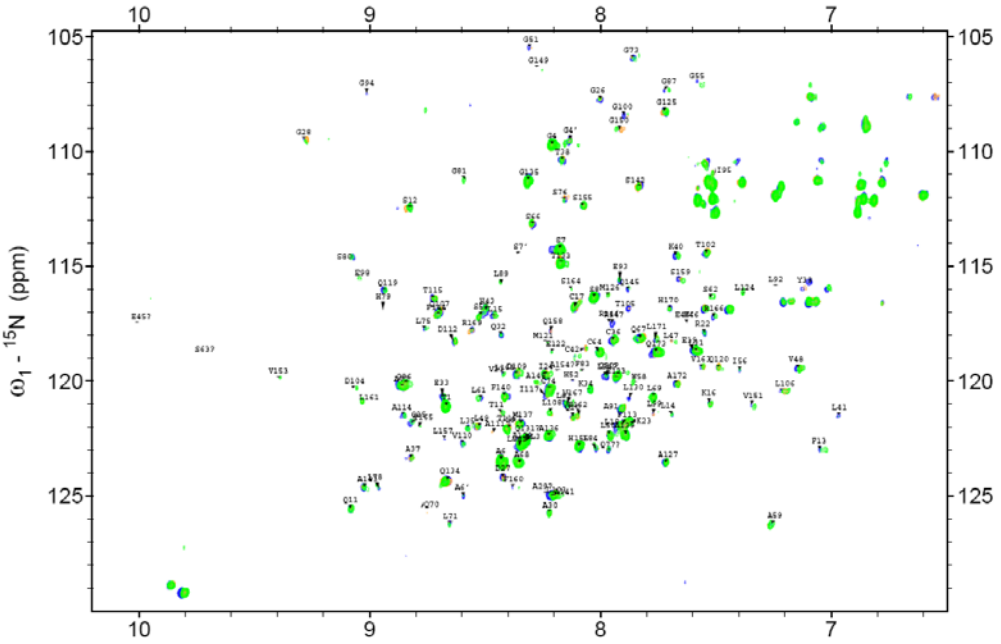


**Figure 10. Overlay of the EP2006 batch V200001 (blue), [US-licensed Neupogen] (orange) and [EU-approved Neupogen] (green) $^{1}H$-$^{15}N$ HSQC spectra in the EP2006 DP formulation**




*Figures excerpted from Sandoz 351(k) BLA submission*

The data derived from the different methods used to assess HOS indicate that the HOS of the three products is highly similar.

**Clarity and sub-visible particles**

The results of the methods used to evaluate clarity and sub-visible particles indicate that both attributes are highly similar in the three products.

**Product-related substances and impurities**

The type and levels of product-related substances and impurities in the three products were assessed quantitatively by the methods listed in Table 1. The results summarized in Table 6 indicate that the three products are highly similar. In addition to the species listed in Table 6, acetylated and phosphogluconoylated species were assessed in EP2006 as well as one other species that might be formed based on the manufacturing process. The results show that these species are absent in EP2006.

**Table 6. Comparison of the type and levels of product-related substances and impurities of EP2006, US-licensed Neupogen and EU-approved Neupogen**

| Species | EP2006 vs US-Neupogen | EP2006 vs EU-Neupogen | US-Neupogen vs EU-Neupogen |
|---|---|---|---|
| High molecular weight species/aggregates | ✓ | ✓ | ✓ |
| Oxidized[a] (five different species) | ✓ | ✓ | ✓ |
| Covalent dimers | ✓ | ✓ | ✓ |
| Partially reduced | ✓ | ✓ | ✓ |
| Formyl-methionine 1 | ✓ | ✓ | ✓ |
| Sequence variant: His→Gln | ✓ | ✓ | ✓ |
| Sequence variant: Asp→Glu | ✓ | ✓ | ✓ |
| Sequence variant: Thr→Asp | ✓ | ✓ | ✓ |
| Succinimide | ✓ | ✓ | ✓ |
| N-terminal truncated (8 different species) | ✓ | ✓ | ✓ |
| Norleucine species[b] (four different species) | ✓ | ✓ | ✓ |
| Deamidated species[c] | ✓ | ✓ | ✓ |

[a] Sites of oxidation are at the methionine residues 1, 122, 127 and 138. Oxidized variants are stability indicating, thus the comparison was conducted on products of similar age
[b] Methionine can be substituted by norleucine at positions 1, 122, 127 and 138
[c] stability indicating, thus the comparison was conducted on products of similar age
✓Same species type and highly similar levels of the species under evaluation

## Comparative stability studies

Comparative stability studies under long term storage conditions, accelerated conditions and stress conditions, including mechanical stress and photostability, were conducted on the three products. A subset of the methods listed in Table 1, including stability indicating methods (e.g., methods to evaluate oxidation, deamidation, and aggregation) were used in the assessment. The results indicate that the three products have similar degradation pathways and degradation products.

### Conclusions on analytical similarity

Based on the data discussed above, EP2006 is analytically highly similar to the reference product, US-licensed Neupogen, notwithstanding minor differences in clinically inactive components.

In addition, EP2006, US-licensed Neupogen and EU-approved Neupogen met the pre-specified criteria for analytical similarity. Sandoz provided a sufficiently robust analysis for the purposes of establishing an analytical bridge between the three products to support the relevance of data generated from clinical and non-clinical studies using of EU-approved Neupogen, to support a demonstration of biosimilarity of EP2006 to the US-licensed reference product.

The analytical data support the scientific bridge based on the relatively simple structure of the protein, the lack of post-translational modifications and the robustness of the analytical characterization, and does not raise residual uncertainty of the results of the analytical similarity studies, when taken together with the other data and information submitted, to support the demonstration of biosimilarity.

# 6 Immunogenicity

### Executive Summary

Immune reactions to therapeutic biological products are mostly caused by antibodies against the drug (anti-drug antibodies; ADA). Therefore, immunogenicity assessment for therapeutic biological products focuses on measuring ADA. In the context of the development program for EP2006, a multi-dose parallel arm study design would allow for the clearest comparison of the immunogenicity of EP2006 to the US-licensed Neupogen and EU-approved Neupogen comparators. This is because, in general, the development of antibodies is enhanced by repeat exposure to an immunogen, and the parallel arm design allows for an immune response to be attributed to a particular product. ADA data from a multidose study with parallel arms comparing EP2006 to US-licensed Neupogen in cancer patients, four multidose cross-over studies comparing EP2006 to US-licensed Neupogen or EU-approved Neupogen, and one single arm study with EP2006 were provided by Sandoz. Because of technical problems with the screening assay used to test samples from the multi-dose parallel arm study, final results from that study were not available at the time of writing of this briefing document. However, the results are expected to be available prior to the Advisory Committee meeting and will be relayed at that time. ADA data from four studies comparing EP2006 to US-licensed Neupogen or EU-approved Neupogen in healthy volunteers and a single arm study of EP2006 in patients revealed no subjects who tested ADA positive. The data indicate that EP2006, US-licensed, and EU-approved Neupogen induce similarly low rates of ADA in treated subjects. However, there is residual uncertainty at this time because, as of the writing of this briefing document, final results were not yet available from a multi-dose parallel arm study.

**Discussion**

An application submitted under section 351(k) of the PHS Act must contain, among other things, information demonstrating that the biological product is biosimilar to a reference product based upon data derived from "a clinical study or studies (including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biological product[10]." Immune responses against therapeutic biological products are a concern because they can negatively impact the drug's safety and efficacy. Unwanted immune reactions to therapeutic biological products are mostly caused by antibodies against the drug (anti-drug antibodies; ADA). Therefore, immunogenicity assessment for therapeutic biological products focuses on measuring ADA.

ADA to EP2006, US-licensed Neupogen, and EU-approved Neupogen were assessed in Study EP06-302, a multidose study with parallel arms comparing EP2006 to US-licensed Neupogen in cancer patients, four multidose cross-over studies comparing EP2006 to US-licensed Neupogen or EU-approved Neupogen, and one single arm efficacy study with EP2006 (EP06-301). As discussed below, Study EP06-302 is the most informative study for assessing similarity in ADA responses since it compares EP2006 to US-licensed Neupogen. However, as of the writing of this document, due to technical difficulties the final results from study EP06-302 are not yet available. Those data should be available prior to the Advisory Committee meeting and will be presented then.

There is a concern that ADA to G-CSF products could diminish the effects of endogenous G-CSF, thereby prolonging or worsening neutropenia. The prescribing information for US-licensed Neupogen states that ADA were detected in 3% of patients receiving US-licensed Neupogen. None of the patients tested positive for neutralizing antibodies. The National Marrow Donor Program[11] reported that there was no difference in the incidence of autoimmune diseases among donors for 6,768 peripheral blood stem cell donations from healthy individuals exposed to G-CSF as compared to 2,726 healthy bone marrow donors not exposed to G-CSF. These data suggest that the incidence of clinically significant neutropenia as a result of ADA that cross react with and inhibit endogenous G-CSF is extremely low.

10. Section 351(k)(2)(A)(i)(I) of the PHS Act. As discussed in the Background section, the statute provides that FDA may determine, in FDA's discretion, that certain studies are unnecessary in a 351(k) application (see section 351(k)(2) of the PHS Act).
11. Pulsipher MA, Chitphakdithai P, Logan BR et al. Lower risk for serious adverse events and no increased risk for cancer after PBSCs BM donation. Blood: 123:3655, 2014

FDA recommends a tiered approach to measuring ADA (draft guidance for Industry: Assay Development for Immunogenicity Testing of Therapeutic Proteins). In the first tier, samples from study subjects are screened for the presence of ADA using a sensitive and specific method. For technical reasons, false negative rates (i.e., the rate at which positive samples test negative) cannot be estimated for ADA assays. However, false positive rates (i.e., the rate that negative samples test positive) can be estimated. Because false negative and false positive rates are related, the false negative rate can be partially controlled by designing the test to have a high false positive rate. Therefore, to reduce the false negative rate for ADA screening assays FDA recommends that the assays have approximately a 5% false positive rate.

In the second tier, samples that screen positive are confirmed to be true positives, and false positives are eliminated. In the third tier, confirmed positive samples are tested for their ability to neutralize the biological activity of the drug, usually in an in vitro bioassay.

Study EP06-302 was a clinical study in cancer patients that included multi-dose parallel arm groups treated either with EP2006 or US-licensed Neupogen. A multi-dose parallel arm study design would allow for the clearest comparison of the immunogenicity of EP2006 to a comparator G-CSF product. This is because, in general, the development of antibodies is enhanced by repeat exposure to an immunogen, and the parallel arm design allows for an immune response to be attributed to a particular product. Study EP06-302 is the most informative study comparing the immunogenicity of EP2006 and US-licensed Neupogen product because it is the only multi-dose parallel arm study in which patients were treated either with EP2006 or a comparator product. Approximately 1583 samples obtained over time from 214 patients were tested in the applicant's ADA screening assay. None of the samples screened positive. Because no sample screened positive, we deduced that the applicant did not adequately set the assay cut-point to account for a 5% false positive rate. The applicant has since reevaluated the study results and established a new cut-point. Using the new cut-point an acceptable number of subjects screened positive. As of the writing of this briefing document, results from the confirmatory assay are still pending. However, the results of the confirmatory assay are expected to be available prior to the Advisory Committee meeting and will be relayed at that time.

Additional information on ADA incidence in EP2006, US-licensed Neupogen and EU-approved Neupogen treated subjects comes from a single arm multi-dose study in EP2006 treated patients and five multidose cross-over comparative studies in healthy volunteers. In the single arm study EP06-301, in which ADA to EP2006 were evaluated in cancer patients, 2.1% of samples tested false positive. There were no true positive samples in that study. This supports a conclusion that multiple doses of EP2006 have low potential to induce immunogenicity. In study EP06-109, in which 28 healthy volunteers were treated with either EP2006 or US-licensed Neupogen, 3.7% of samples tested false positive and none tested true positive. Three healthy volunteer studies in which EP2006 was compared to EU-approved Neupogen, EP06-101, EP06-103, and EP06-105, had false positive rates that ranged from 2.7% to 4.1%. No true positive samples were detected in any of those studies. In study EP06-102, three samples,

including a pretreatment sample, from the same subject confirmed positive. However, there were no false positive samples in that study, so the true incidence may be under estimated. Overall, results from studies in which the assay had approximately a 5% false positive rate show no evidence of ADA being induced either by EP2006, US-licensed Neupogen, or EU-approved Neupogen.

In summary, there is residual uncertainty about whether ADA incidence is similar in subjects administered EP2006 and either US-licensed Neupogen or EU-approved Neupogen because comparative data are available from only cross-over design studies. This uncertainty is mitigated by data indicating that neither EP2006 nor the Neupogen products induced ADA in treated subjects. The residual uncertainty should be further addressed by the requested new data from study EP06-302 comparing the incidence of ADA development in EP2006 and US-licensed Neupogen treated patients. Those data should be available prior to the Advisory Committee meeting and will be presented then. To date, the data indicate that EP2006 and EU-approved Neupogen are similar in that neither drug induced ADA in treated subjects.

# 7 Pharmacology/Toxicology

### Executive Summary

EP2006 was compared head-to-head with EU-approved Neupogen in animal studies to assess the pharmacodynamics (PD), toxicity, toxicokinetics (TK) and local tolerance of the products. The selection of the subcutaneous (SC) route of administration, and dose levels between 10 and 500 mcg/kg, allowed for a meaningful evaluation of the potential differences between EP2006 and EU-approved Neupogen in animals. The nonclinical pharmacology and toxicology data submitted demonstrate that similar exposures were attained, very similar PD effects were observed, and the same target organs of toxicity were identified in the comparative animal studies of EP2006 and EU-approved Neupogen. Analytical bridging studies (see CMC section above for details) comparing EP2006, EU-approved Neupogen, and US-licensed Neupogen established that all three products are similar at the physiochemical level. From the perspective of nonclinical pharmacology and toxicology, no residual uncertainties regarding the similarity of EP2006 to the reference product.

### Discussion

The animal pharmacology and toxicology studies submitted to the application were assessed with respect to the similarity of toxicities between EP2006 and EU-approved Neupogen as well as with regards to the similarity other biological responses (e.g., systemic exposure and PK/PD) between the two products. The submitted studies were determined to be acceptable for this analysis since recombinant human G-CSF is not species specific (making animal studies relevant to predicting potential effects in humans), and because the studies were all in compliance with internationally

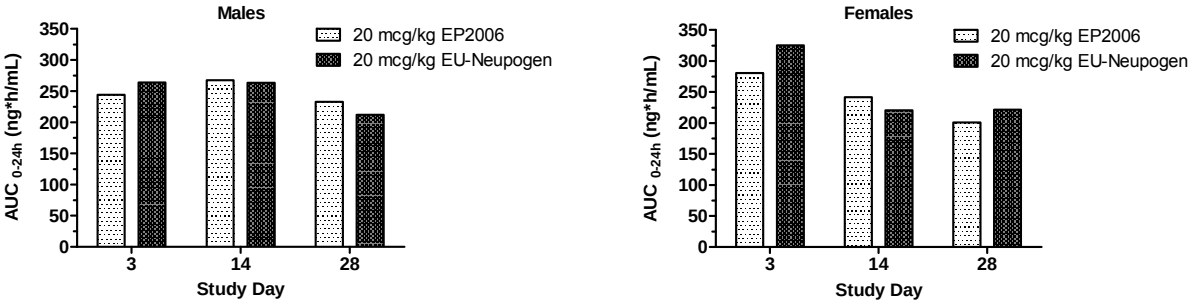
recognized standards (i.e., Organization for Economic Co-operation and Development (OECD)) pertaining to the design and conduct of nonclinical studies according to Good Laboratory Practice. The nonclinical review found that the particular species, doses, regimens, and duration of exposure selected by the Applicant were based on contemporary methods used to assess the relevant properties of new drugs in addition to our general understanding of G-CSF pharmacology and toxicology.

Two of the submitted studies were pivotal to the nonclinical safety evaluation for EP2006; the single dose local tolerance study conducted with the test articles, and the 28-day repeat-dose toxicology study using the commercial formulation (containing an L-glutamic acid buffer). The local tolerance study (EP06-003) was conducted in New Zealand White Rabbits to assess for potential erythema, edema, hematomas, pain reactions, gross pathology, and histopathology in rabbits administered 500 mcL of undiluted EP2006 or EU-approved Neupogen via the subcutaneous (SC), intravenous (IV), perivascular (PV), intraarterial (IA) and intramuscular (IM) routes. The minimal findings in rabbits administered EP2006 (SC) or EU-approved Neupogen (SC) were indistinguishable from those observed in control rabbits administered saline (SC), and no other definitive drug-related changes occurred, indicating EP2006 is as safe as EU-approved Neupogen at the SC injection site.

The 28-day SC injection toxicology study with a 6-week recovery period (EP06-006) was conducted in Wistar rats administered 20, 100 or 500 mcg/kg EP2006 or 20 or 500 mcg/kg EU-approved Neupogen. Similar dose-related increases in white blood cells (notably neutrophils) were observed in males and females treated with 20 mcg/kg or more of EP2006 or EU-approved Neupogen at several timepoints throughout the course of the study. Other noteworthy findings were similar between EP2006 and EU-approved Neupogen and related to the pharmacology of the products, specifically: dose-related reversible increases in spleen weights; and hyperplasia of myeloid cells, increased hematopoietic cells in the bone marrow and spleen, and myeloid hyperplasia in the liver, all of which occurred with similar incidence, severity, and reversibility following administration of either product.

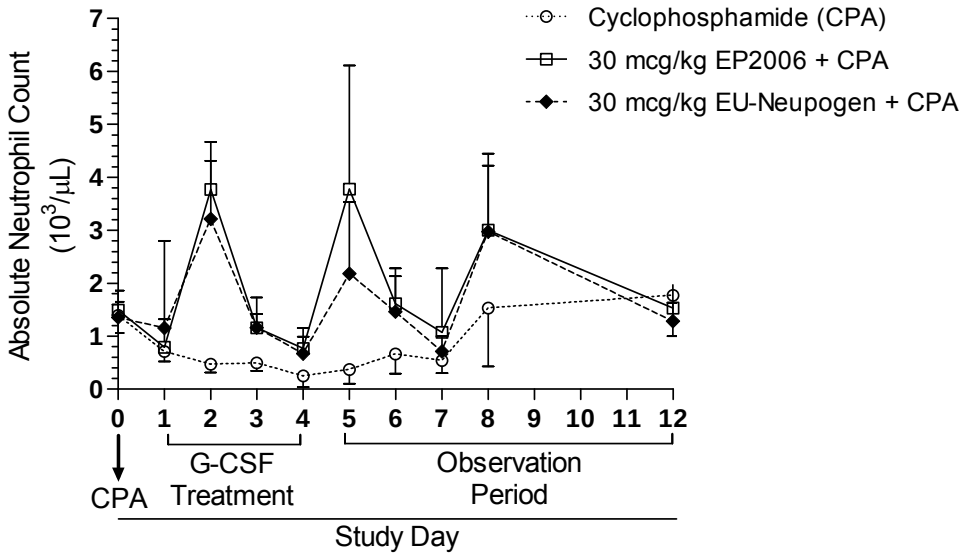
Exposures to G-CSF were measured at several timepoints throughout the 28-day study in rats receiving equivalent dose levels of EP2006 or EU-approved Neupogen. As shown below (Figure 11), exposures were very similar in males and similar in females administered 20 mcg/kg of EP2006 or EU-approved Neupogen on Days 3, 14, and 28. The minimal differences in exposure that were observed between the two products are unlikely to translate into any clinically meaningful differences, given that anti-G-CSF antibody responses were detected in rats from the Day 14 timepoint onwards, and that immunogenicity in animals is generally not predictive of immunogenicity in humans. EP2006 dosing solutions had slightly less G-CSF content than EU-approved Neupogen solutions. The exposure data ($AUC_{0\text{-}24h}$) generated with the 20 mcg/kg SC doses of EP2006 or EU-approved Neupogen were paid special attention because these exposures most closely reflect the $AUC_{0\text{-}24h}$ values measured in patients given clinically relevant doses of the products.

**Figure 11. Exposure ($AUC_{0-24h}$) to G-CSF in Rats Repeat Dosed with EP2006 or EU-approved Neupogen (Study EP06-006)**




The similarity of EP2006 to EU-approved Neupogen was exemplified in the PD study (EP06-004) which examined the neutrophil response in chemotherapy (Day 0)-induced neutropenic rats for 8 days following administration of 30 mcg/kg of either EP2006 or EU-approved Neupogen on Days 1 to 4 (Figure 12). Both EP2006 and EU-approved Neupogen produced very similar distinctive biphasic increases in neutrophil counts in the neutropenic rats exposed to 30 to 100 mcg/kg with two peak responses occurring on Days 2 and 5 with lower values on Days 3-4 and 6-12.

**Figure 12. Neutrophil Response in a Chemotherapy-induced Neutropenic Rat Model Dosed with EP2006 or EU-approved Neupogen (Study EP06-004)**



In summary, the animal studies submitted demonstrate the similarity of EP2006 to EU-approved Neupogen in terms of pharmacokinetics, pharmacodynamics, and toxicity in animals. From the perspective of pharmacology and toxicology the results of these animal studies can be taken together with the data from the analytical bridging studies (see CMC section above for details) to demonstrate EP2006 is also similar to the reference product US-licensed Neupogen. No residual uncertainties have been identified by the discipline.

# 8 Clinical Pharmacology

### Executive Summary

The applicant submitted four pharmacokinetic (PK) and pharmacodynamic (PD) studies that evaluated subcutaneous (SC) doses between 1-10 mcg/kg in healthy subjects to evaluate the PK and PD similarity of EP2006 with US-licensed Neupogen. In addition to PK, these studies evaluated absolute neutrophil counts (ANC) and CD34+ cell counts as PD markers. Among these, three studies utilized EU-approved Neupogen. As such, adequate data and information was needed to scientifically justify the relevance of these comparative data to an assessment of biosimilarity to the US-licensed reference product. As noted above, the pairwise comparisons of EP2006, US-licensed Neupogen and EU-approved Neupogen met the pre-specified criteria for analytical similarity for the purposes of establishing an analytical bridge to justify the relevance of the data generated using EU-approved Neupogen.

The 90% CI for AUC and $C_{max}$ after a single dose were within the pre-defined limits of 80-125%. Similarly, the 95% CI for AUEC and $ANC_{max}$ for ANC after single dose were within the pre-defined limits of 80-125%. The 95% CI for AUEC and $CD34_{max}$ for CD34+ after multiple doses were within the limits of 80-125%. Overall, the PK and PD studies support a demonstration of PK and PD similarity between EP2006 and US-licensed Neupogen.

### Description of All Clinical Studies

The PK and PD of EP2006 following SC administration have been characterized in studies that include either US-licensed Neupogen or EU-approved Neupogen as the comparator (Table 7). The summary of each study design including PK and PD endpoints are described below.

- Study EP06-109 was a randomized, double-blind, two-way cross-over study to determine the PK, PD, and safety of EP2006 and US-licensed Neupogen following a single 10 mcg/kg SC dose in healthy subjects (N=28). The PK endpoints for this study were single dose $AUC_{0\text{-last}}$ and $C_{max}$. The single dose PD endpoints were ANC $AUEC_{0\text{-}120h}$ and $ANC_{max}$.

- Study EP06-302 was a randomized, double-blind, parallel-group, multi-center study comparing the efficacy and safety of EP2006 and US-licensed Neupogen (5 mcg/kg SC) in patients with breast cancer treated with myelosuppressive chemotherapy (N=204). A PK sub-study was included in this study to characterize the PK of a single 5 mcg/kg SC dose in patients in Cycle 1 (n=54). Trough concentrations were also collected throughout Cycle 1 through Cycle 2 pre-dose.

- Study EP06-103 was a randomized, double-blind, multiple-dose, two-way cross-over study to determine the PD and PK of EP2006 and EU-approved Neupogen at two dose levels administered to two groups (2.5 and 5 mcg/kg) as single and multiple SC injections to healthy subjects (N=28/dose). The PK endpoints for this study were single dose $AUC_{0\text{-}24h}$ and $C_{max}$. The single dose PD endpoints were ANC $AUEC_{0\text{-}24h}$ and $ANC_{max}$. The multiple dose PD endpoints were CD34+ $AUEC_{0\text{-}216h}$ and $CD34_{max}$.

- Study EP06-105 was a randomized, double-blind, two-way cross-over study to determine the PK and PD of EP2006 and EU-approved Neupogen administered at a single 1 mcg/kg SC dose to healthy subjects (N=24). The PK endpoints for this study were single dose $AUC_{0\text{-}24h}$ and $C_{max}$. The single dose PD endpoints were ANC $AUEC_{0\text{-}24h}$ and $ANC_{max}$.

- Study EP06-101 was a randomized, double-blind, multiple-dose, two-way cross-over study to compare the PK, PD, and safety of EP2006 and EU-approved Neupogen following single and multiple 10 mcg/kg SC doses in healthy subjects (N=32). The PK endpoints for this study were single dose $AUC_{0\text{-}24h}$ and $C_{max}$. The multiple dose PD endpoints were CD34+ $AUEC_{0\text{-}216h}$ and $CD34_{max}$.

**Table 7. Summary of relevant EP2006 clinical studies**

| Study (Dates) | Design Features | Objectives | Dose/Route/Duration |
|---|---|---|---|
| **Studies using US-licensed Neupogen (the reference product)** | | | |
| **EP06-109** (25-Feb-2011 to 22-Apr-2011) | Randomized, double-blind 2-way crossover in HS (N=28) | 1. ANC, PK<br>2. $CD34^+$, safety | 10 mcg/kg, SC single dose |
| **EP06-302** (26-Dec-2011 to 17-Jun-2013) | Randomized double-blinded, active controlled study (N=204) | 1. Safety, efficacy<br><br>Included a Cycle 1 PK sub-study (n=54) | 5 mcg/kg, SC multiple dose |
| **Studies using EU-approved Neupogen** | | | |
| **EP06-103** (29-Aug-2006 to 05-Dec-2006) | Randomized, double-blind, 2-way crossover in HS, with two dose groups (N=28/dose) | 1. ANC<br>2. PK, $CD34^+$, safety | 2.5 & 5 mcg/kg, SC single and multiple (7d) dose |
| **EP06-105** (21-Apr-2008 to 26-May-2008) | Randomized, double blind, 2-way crossover in HS (N=24) | 1. ANC<br>2. PK, safety | 1 mcg/kg, SC single dose |
| **EP06-101** ( 25-Oct-2004 to 12-Apr-2005) | Randomized, double-blind, 2-way crossover in HS (N=32) | 1. PK<br>2. CD34+, ANC, safety | 10 mcg/kg, SC single and multiple (7d) dose |

HS, healthy subjects; ANC; absolute neutrophil count; PK, pharmacokinetics; SC, subcutaneous

**PK/PD Study Design Rationale**

As is described in the draft guidance for Industry entitled, "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product"[12], for PK similarity assessments, a single-dose, randomized, crossover study is generally the preferred design. Furthermore, a cross-over study design is recommended for products with short half-life (e.g., less than 5 days), rapid PD response, and low incidence of immunogenicity. For PD similarity assessments, multiple doses may be appropriate when the PD effect is delayed or otherwise not parallel to the single-dose drug PK profile.

Based on the US-licensed Neupogen labeling[13] and data described in published literature[14], the terminal half-life for G-CSF ranges from 3.5-9 hours. Rapid increase in absolute neutrophil counts (ANC) is observed in healthy subjects within 24 hours after single dose G-CSF administration[14]. Significant increase in CD34+ cells is observed in healthy subjects following 5 daily doses of G-CSF with significant increase after day 4 and maximum CD34+ counts achieved on day 6[15]. As is described in the US-licensed Neupogen labeling, the incidence of immunogenicity is 3%[13]. Given the short half-life, rapid ANC response after single dose, and low incidence of immunogenicity, a cross-over design for PK and ANC similarity is justified. Given that a robust CD34+ response is observed in healthy subjects after multiple doses of G-CSF, a multiple dose study for CD34+ similarity is justified.

**Study Population Justification**

As is described in the draft guidance"[12], human PK and PD similarity studies should be conducted in healthy volunteers if the product can be safely administered to this population. A study in healthy volunteers is considered to be more sensitive in evaluating similarity between products because the population is likely to produce less PK variability compared with that in patients with potentially confounding factors such as underlying disease and concomitant medications.

12. Guidance for Industry "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product." May 2014. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf

13. Neupogen Labeling approved on September 13, 2013 found at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/103353s5157lbl.pdf.

14. Borleffs, et al. Effect of Escalating Doses of Recombinant Human Granulocyte Colony-Stimulating Factor (Filgrastim) on Circulating Neutrophils in Healthy Subjects. Clinical Therapeutics (1998) 20:722-36.

15 Stroncek, et al. Treatment of normal individuals with granulocyte-colonystimulating factor: donor experiences and the effects on peripheral blood CD34+ cell counts and on the collection of peripheral blood stem cells. Transfusion (1996) 36:601-10.

Based on published literature[14-16], G-CSF has been safely administered to healthy subjects as single and multiple doses up to 10 mcg/kg/day for 10 days. Following single and multiple dose administrations of G-CSF in healthy subjects, significant increases in peripheral blood neutrophils and CD34+ cell counts are observed, respectively[14-16]. Based on the data regarding US-licensed Neupogen submitted in this application, the coefficient of variation (CV%) on PK exposure (AUC) was around 20% in healthy subjects in study EP06-109 and around 40% in patients with breast cancer in study EP06-302 justifying that a healthy subject study is likely to be more sensitive and less confounded by patients factors and treatment intervention. The CV% of AUEC of ANC in healthy subjects ranged between 16 - 25% and in patients was ~40%.

The mechanism of action and pharmacologic properties of US-licensed Neupogen are fundamentally the same in healthy subjects and patients with neutropenia. The clinical relevance of the PD markers is discussed in detail later in the "Clinical Relevance of PD Endpoints" section. Given that ANC is a relevant marker for G-CSF products in PD studies and the fact that bone marrow in healthy subjects, in contrast to patients who are receiving chemotherapy, is more responsive to G-CSF treatment makes a healthy subject study a sensitive model for G-CSF activity assessment than a study in patients with cancer treated with chemotherapy.

Additionally, since single and multiple doses of G-CSF may be safely administered to healthy subjects, human PK and PD similarity studies may be conducted in this population. Overall, the PK and PD similarity studies conducted in healthy subjects are justified.

**Intra- and inter-subject PK and PD variability**

The applicant took into account intra-subject coefficients of variation (CV%) for the PK and the PD parameters of interest when determining the sample sizes of the PK and PD similarity studies. For example, the sample size in study EP06-109 (single SC dose 10 mcg/kg) was estimated using intra-subject CV% data from a previously completed study EP06-101 comparing single and multiple SC doses of 10 mcg/kg of EP2006 and EU-approved Neupogen. Overall, all PK and PD similarity studies (EP06-109, EP06-103, EP06-105 and EP06-101) had sufficient sample size for demonstration of PK and PD similarity. The PK substudy in EP06-302 was not intended to evaluate PK similarity and did not have sufficient sample size given the higher variability in patients.

**PK and PD measurements**

PK (AUC and $C_{max}$) was assessed following a single dose out to 24 to 48 hours post-dose, which captures at least 5 half-lives of G-CSF, and is acceptable.

16 . Gascon, et al. Development of a new G-CSF product based on biosimilarity assessment. Annals of Oncology (2010) 21:1419-1429.

ANC (AUEC and $ANC_{max}$) was assessed following a single dose out to 120 hours post-dose, which captured at least 80% of the ANC area under the effect curve (AUEC) profile, and is acceptable.

CD34+ (AUEC and $CD34_{max}$) was assessed following seven daily doses out to 216 hours post the final dose, which captured at least 80% of the CD34+ area under the effect curve (AUEC) profile, and is acceptable.

**PK and PD Endpoints and Assays**

The endpoints used for PK (single dose AUC and $C_{max}$) and PD (single dose ANC AUEC and $ANC_{max}$ and multiple dose CD34+ AUEC and $CD34_{max}$) measures had precision and sufficient sensitivity to detect clinically meaningful differences between EP2006 and the comparator, should they exist. The assays used to evaluate PK and PD (ANC and CD34+) were validated. Details about the various assays are below.

PK assay: To quantify concentrations of rhG-CSF in human serum, an enzyme-linked immunosorbent assay (ELISA) kit was used. The ELISA was validated over a concentration range of 39 pg/mL to 2.50 ng/mL.

PD assays:
- ANC was measured with hematology analyzers or flow cytometry.
- CD34+ was measured with flow cytometry.

**PK and PD Predefined Similarity Margin Selection**

In all studies, the predefined similarity criteria for both AUC and $C_{max}$ were that the 90% CI of the ratio should lie within 80-125% except for EP06-101 where a wider margin of 75-133% for $C_{max}$ was pre-defined. The margin of 80-125% proposed by the applicant is acceptable. This criterion has been generally used for bioequivalence assessment of generic drugs and for biocomparability evaluation of biological products for pre- and post-approval manufacturing process[17].

For ANC, the predefined similarity criteria for both AUEC and $ANC_{max}$ were that the 95% CI for the ratio of the geometric means should lie within 80-125% in studies EP06-109 and EP06-105. In study EP06-103, the applicant used tighter predefined criteria that 95% CI for the ratio should lie within 87.25-114.61% for the 2.5 mcg/kg dose and 86.50-115.61% for the 5 mcg/kg dose. The applicant also presented the 90% CI for the ratio of the geometric means of the exposure parameters for the test and reference products.

17 . Guidance for Industry "Statistical Approaches to Establishing Bioequivalence". January 2001. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070124.pdf.

Applicant's pre-defined criteria are acceptable as it is tighter and more conservative than the standard criteria of 90% CI of the ratio to lie within 80-125%. Additionally as explained below under the "Clinical Relevance of the PD Endpoints" section, a 20% difference in the ANC AUEC is not likely to translate into a clinically meaningful difference in effectiveness.

For CD34+, there were no predefined criteria for similarity. However, the applicant did report the 95% CI and 90% CI for the ratio of the exposure parameters (AUEC and $CD34_{max}$).

**Clinical Relevance of the PD Endpoints**

As is described in the draft guidance for Industry entitled, "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product"[12], PD measures should reflect the mechanism of drug action. PD measure should have a wide dynamic range over the range of drug concentrations achieved during the PK study.

**Absolute Neutrophil Count (ANC)**

ANC is a relevant PD marker for G-CSF as it reflects the mechanism of action (MOA) of G-CSF. US-licensed Neupogen is indicated to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy and for other indications. Neutropenia is generally defined by abnormally low neutrophils in the blood that increases the risks for infection and other complications. Duration of severe neutropenia (DSN) was considered a clinically relevant endpoint for the approval of US-licensed Neupogen[13]. Additionally incidence of infection is considered as a clinically relevant outcome in the clinical trial used to support approval of US-licensed Neupogen[13].

Bodey et al.[18] demonstrated that in patients receiving chemotherapy, the percentage of patient days with infection decreased as granulocyte levels increased. A similar relationship between the severity of infection and granulocyte levels was also observed.

Based on data from the US-licensed Neupogen arm in Cycle 1 from the study EP06-302, ANC AUEC is correlated with the primary endpoint of DSN, as shown in Figure 11A. DSN decreases with increasing ANC AUEC. This correlation was quantified using a Poisson regression model. The model fit the data reasonably well as shown in Figure 11B. The parameters from the Poisson regression model are summarized in Table 8.

Furthermore, using the quantitative relationship developed, simulations were carried out to illustrate the sensitivity of ANC AUEC to detect potential clinically meaningful differences in effectiveness of products. For these simulations, the mean ANC AUEC

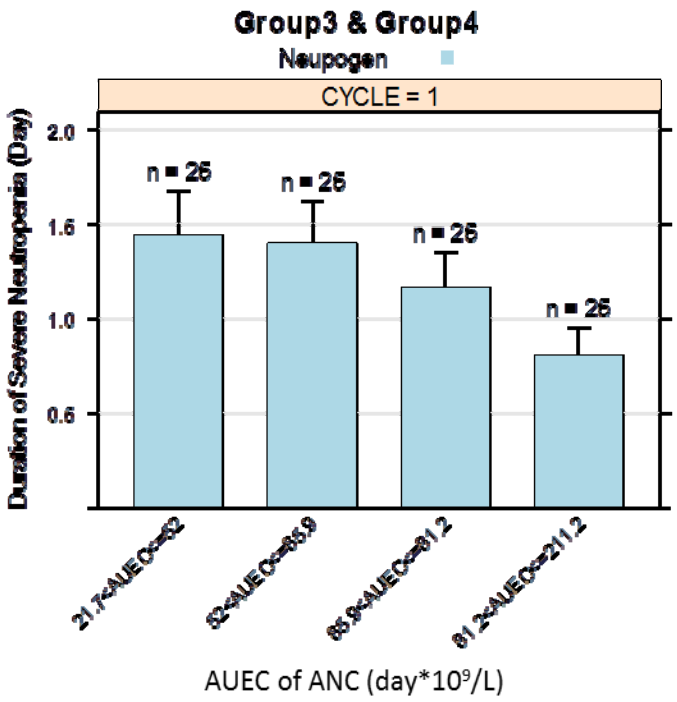
18. Bodey, et al. Qualitative Relationships between Circulating Leukocytes and Infection in Patients with Acute Leukemia. Annals of Internal Medicine (1966) 64:328-340.

was varied from -50% to 50%. Scenarios where the difference in the PD between two products (e.g., test and the reference product) varied across this range were simulated. The mean differences in DSN between the products was calculated using the Poisson model.

Simulation results, illustrated in Figure 14 show that a ± 20% difference in the ANC AUEC between the test and the reference would translate into a mean difference in DSN of less than ± 0.2 days between the products. A difference of ± 1 day between products is generally considered not to be a clinically meaningful difference for DSN. Additionally, even with a larger difference of ± 50% in the ANC AUEC between the test and the reference, the predicted mean difference in DSN between the products is within ± 1 day. This suggests that the ANC AUEC is a more sensitive endpoint to detect differences between products than the clinical endpoint, DSN.

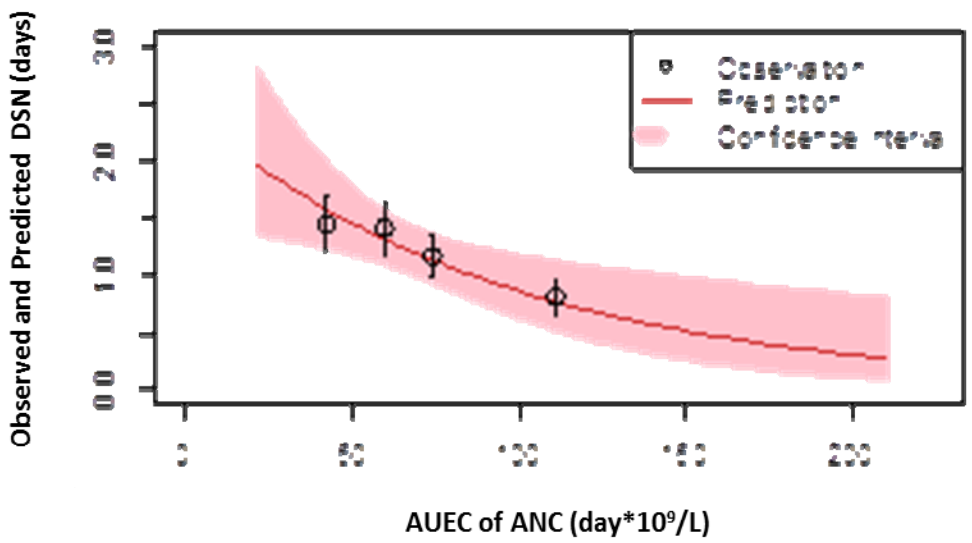
**Figure 13. Correlation between AUEC of ANC (day*$10^9$/L) and DSN (days) for US-licensed Neupogen in study EP06-302**

**A.**




AUEC represents the area under the ANC curve from day 1 to day 10. Patients were divided in 4 quartiles based on their ANC AUEC and their mean (SE) DSN were calculated and plotted for the 4 groups in the plot above.

**B.** Observed and Predicted DSN versus AUEC of ANC



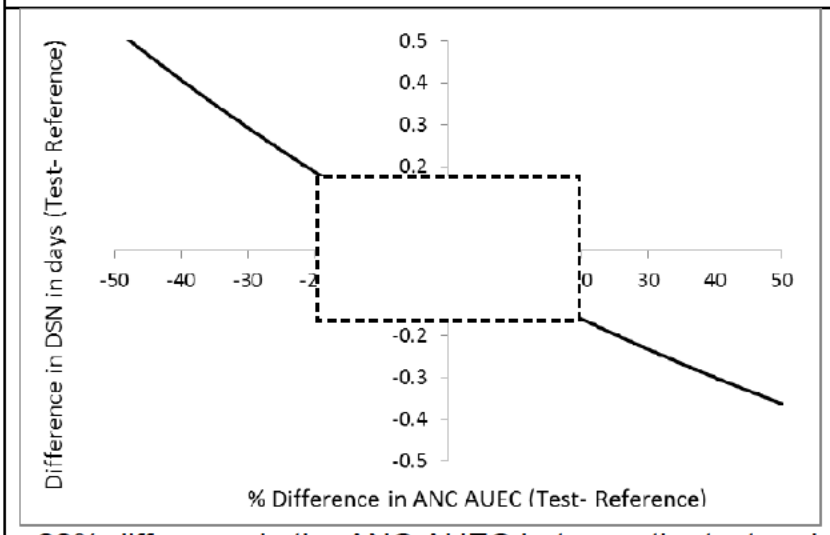

Diagnostic plot suggesting reasonable fit of the Poisson regression model to the observed data

**Table 8. Parameter Estimates of the Poisson Regression Model for DSN**

| Parameter | Estimates | Std. Error | p-value |
|---|---|---|---|
| Intercept | 0.897 | 0.262 | 0.0006 |
| AUEC of ANC* | -0.0105 | 0.004 | 0.006 |

*With 10 unit increase (i.e., $10*10^9$ day/L increase) in AUEC of ANC, the mean DSN would decrease by a factor of exp(-0.0105*10)=0.9 (e.g., from 1 day to 0.9 day)

**Figure 14. Plot to illustrate the sensistivity of ANC AUEC to detect clinically meaningful differences in effectiveness in terms of duration of severe neutropenia between products**




±20% difference in the ANC AUEC between the test and the reference would translate into a mean difference in DSN of less than ±0.2 days as represented by the shaded region

## CD34+ Cell Count

CD34+ cell count is a relevant PD marker as it reflects the MOA of US-licensed Neupogen for peripheral blood progenitor cell mobilization. US-licensed Neupogen is indicated for peripheral blood progenitor cell collection (PBPC) and therapy in cancer patients[13]. Based on the FDA approved drug label for US-licensed Neupogen[13], CFU-GM was used as the marker for engraftable PBPC. The total number of CFU-GM and/or CD34+ cells collected was a significant predictor of platelet recovery. CFU-GM and CD34+ cells follow a similar time profile[13] (Figure 15). Also, CD34+ cell levels correlate with CFU-GM cell levels[19] (Figure 16). Therefore, the effects on stem cell mobilization can be reliably assessed and compared based on CD34+ cell counts.

19 . Dazzi et al. Relationships between total CD34+ cells reinfused, CD34+ subsets and engraftment kinetics in breast cancer patients. Hematologica (2000) 85:396-402. Obtained from the Haematologica Journal website http://www.haematologica.org.

Figure 15. Data from US-licensed Neupogen labeling for CFU-GM and CD34+ profiles following multiple 10 mcg/kg SC doses of US-licensed Neupogen[13]

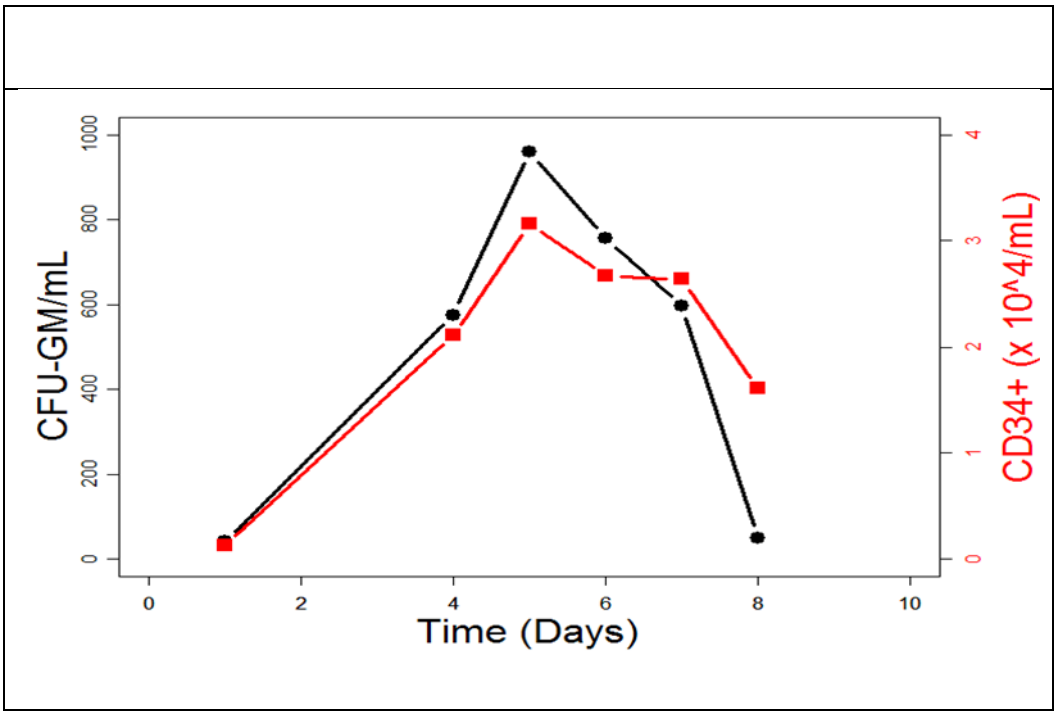
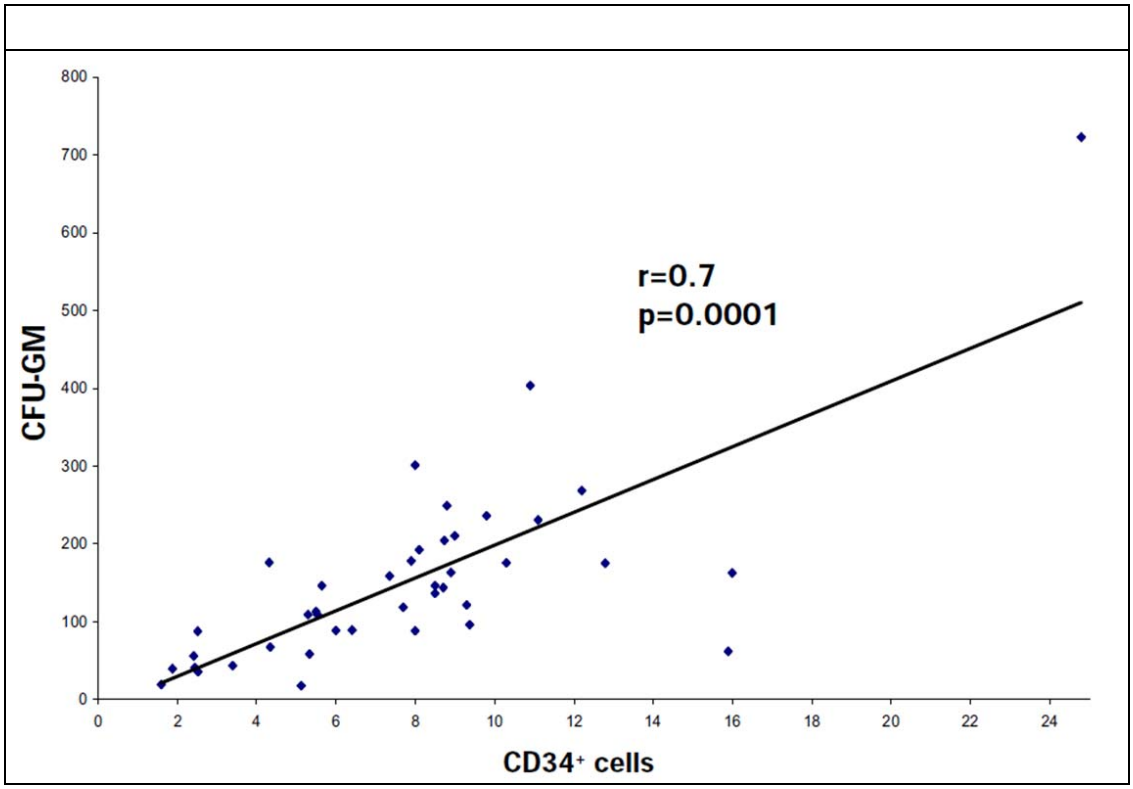


**Figure 16. Literature data demonstrating correlation between total CD34+ cell count (x10$^6$/kg/bw) and CFU-GM (x10$^4$/kg/bw)[21]**



**The Reference Product**

The BPCI Act defines the "reference product" as the single biological product licensed under section 351(a) of the PHS Act against which a proposed biosimilar product is evaluated in a 351(k) application (see section 351(i)(4) of the PHS Act). As a scientific matter, analytical studies and at least one clinical PK and, if appropriate, PD study, intended to support a demonstration of biosimilarity must include an adequate comparison of the proposed biosimilar product directly with the US-licensed reference product[12]. An applicant may use a non-US-licensed comparator product in certain studies to support a demonstration that the proposed biological product is biosimilar to the US-licensed reference product[12]. If an Applicant seeks to use data from a clinical study comparing its proposed biosimilar product to a non-US-licensed product to address, in part, the requirements under section 351(k)(2)(A) of the PHS Act, the applicant should provide adequate data or information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the US-licensed reference product. As a scientific matter, the type of bridging data needed will always include data from analytical studies (e.g., structural and functional data) that directly compares all three products [i.e., the proposed biosimilar product (EP2006), the US-licensed reference product (US-licensed Neupogen), and the non-US-licensed comparator product (EU-approved Neupogen)] and is likely to also include PK and, if appropriate, PD study data for all three products[12].

The applicant used the reference product, US-licensed Neupogen[13], in one single dose PK and PD clinical study (EP06-109) and the comparative efficacy and safety study (EP06-302). The applicant used EU-approved Neupogen as the comparator in single and multiple dose PK and PD clinical studies (EP06-101, -103, and -105). The applicant utilized analytical bridging studies (e.g., structural and functional data) that directly compared all three products (i.e., EP2006, the US-licensed Neupogen, and EU-approved Neupogen) to justify the relevance of the data generated using EU-approved Neupogen for a demonstration of biosimilarity to the US-licensed reference product. Refer to the CMC section above for details. Given the relatively simple structure of G-CSF, other product-specific considerations and the robustness of analytical data provide as described in the CMC section, availability of robust and sensitive analytical assays, and breadth of clinical data submitted, a 3-way analytical bridge is considered acceptable for this program to provide an adequate scientific bridge.

**Selecting the Route of Administration**

As is described in the draft guidance for Industry entitled, "Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product"[12], the subcutaneous or the extravascular route of administration is generally considered more sensitive because it can provide insight into potential PK differences during the absorption phase in addition to the distribution and elimination phases. The clinical

studies described in Table 7 utilized the subcutaneous route of administration and are acceptable.

**Dose Selection Rationale**

Pharmacokinetic Basis

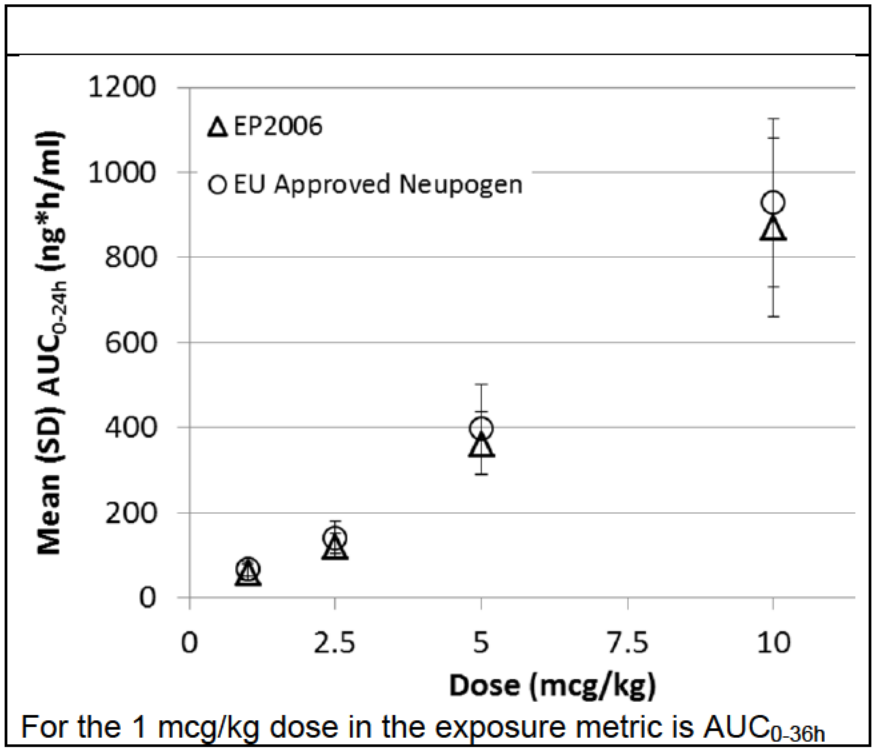
A cross-study comparison using G-CSF data from the EP2006 application, where single SC doses of 1-10 mcg/kg were studied in healthy subjects, revealed increasing G-CSF exposure ($AUC_{0-24h}$) with increasing dose (Figure 17). Doubling the dose resulted in approximately 2-fold or greater increase in AUC.

Similarly, a literature report also showed that single SC doses of 75-600 mcg (equivalent to 1-8 mcg/kg for a 70 kg subject, respectively) resulted in 2-fold increases in G-CSF exposure ($AUC_{0-24h}$) as the dose was doubled[19]. Furthermore, in patients (n=5), an increase in G-CSF concentration was observed following SC doses of 10, 30 and 60 mcg/kg[20].

Given the observed trend for increases in exposure in healthy subjects following SC administration of single doses up to 10 mcg/kg, a G-CSF SC single dose of up to 10 mcg/kg appears reasonable for demonstrating PK similarity.

20. Gabrilove, et al. Phase I Study of Granulocyte Colony-Stimulating Factor in Patients with Transitional Cell Carcinoma of the Urothelium. Journal of Clinical Investigation (1988) 82:1454-61.

**Figure 17. Dose vs. PK exposure for EU-approved Neupogen and EP2006 in healthy subjects at single SC doses of 1-10 mcg/kg in studies EP06-101, -103, -105**




PD Basis: Absolute Neutrophil Count (ANC)

An increase in AUEC of ANC is observed with increasing single SC doses of 1 mcg/kg and 10 mcg/kg in healthy subjects (data from EP2006 application) (Table 9). The dose-response in Table 9 should be viewed cautiously as data are being compared between different studies.

**Table 9. Dose vs. ANC exposure for Neupogen and EP2006 in healthy subjects at single SC doses of 1 mcg/kg and 10 mcg/kg in studies EP06-105, and -109, respectively.**

| Study | Dose (mcg/kg) | Geometric mean ANC $AUEC_{0-120h}$ ($10^9$*h/L) | |
|---|---|---|---|
| | | EP20006 | Neupogen* |
| EP06-105 | 1 | 741 | 725 |
| EP06-109 | 10 | 1524 | 1472 |

*Study EP06-105 used EU-approved Neupogen and EP06-109 used US-licensed Neupogen

A literature report of within study comparison of single SC5 mcg/kg and 10 mcg/kg doses of EU-approved Neupogen in healthy subjects also demonstrated a trend for

increased ANC AUEC as the dose increased[21]. In patients, dose-dependent increase in ANC over baseline was also observed after multiple SC doses of 1-60 mcg/kg[20].

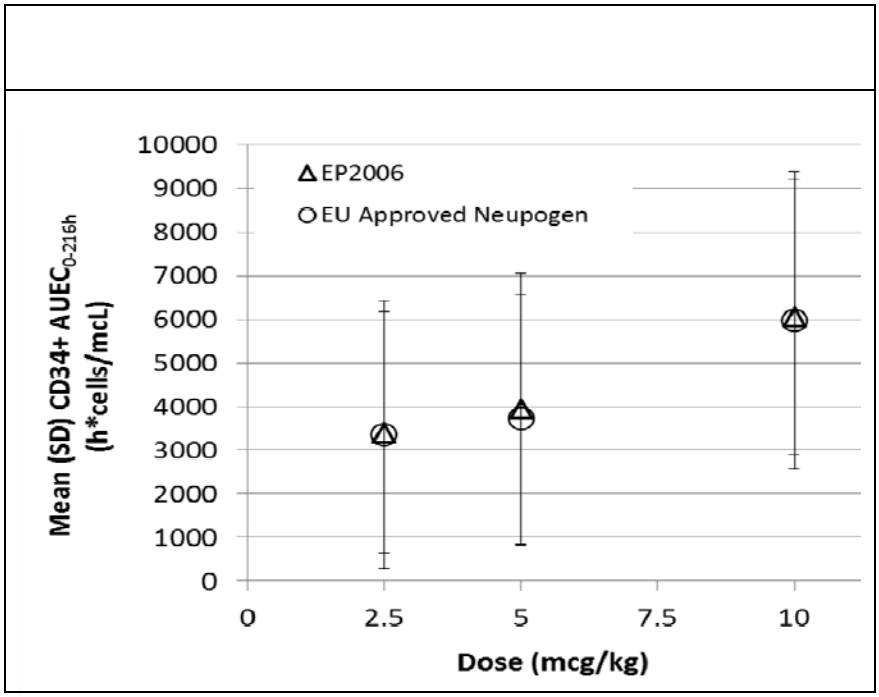
Given the observed trend for increases in AUEC of ANC in healthy subjects following SC administration of single doses up to 10 mcg/kg, a G-CSF SC single dose of up to 10 mcg/kg appears reasonable for demonstrating ANC similarity.

PD Basis: CD34+ Cell Count

A trend for increase in AUEC of CD34+ cell count is observed in healthy subjects following multiple SC doses of 2.5-10 mcg/kg of EU-approved Neupogen and EP2006 (Figure 18). Similarly, a trend for increase in CD34+ cell count with increasing doses (2-10 mcg/kg) of US-licensed Neupogen administered for 5 days in healthy donors was also reported in published literature[15].

Given the observed trend for increases in AUEC of CD34+ cell count in healthy subjects following SC administration of multiple doses up to 10 mcg/kg, a G-CSF SC multiple dose of up to 10 mcg/kg appears reasonable for demonstrating CD34+ cell count similarity.

**Figure 18. Dose vs. CD34+ exposure in healthy subjects following repeated (7 daily) SC doses of EU-approved Neupogen and EP2006 in studies EP06-101, -103**




21. Lubenau et al. Pharmacokinetic and Pharmacodynamic Profile of New Biosimilar Filgrastim XM02 Equivalent to Marketed Filgrastim Neupogen. Biodrugs (2009) 23:43-51.

**Summary of EP2006 PK and PD Results**

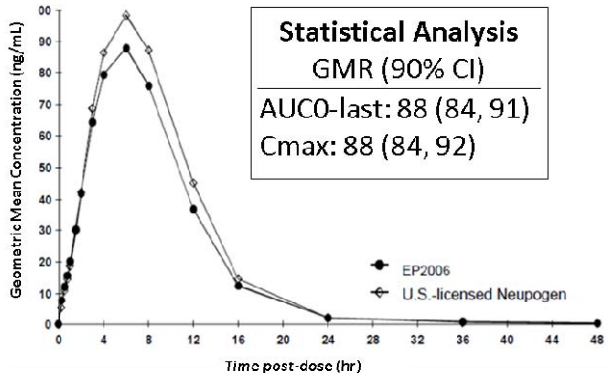
The human PK and PD studies demonstrated PK and PD (ANC and CD34+) similarity between EP2006 and the US-licensed Neupogen and EU-approved Neupogen in healthy subjects.

Given that the applicant is seeking to use data from clinical studies comparing EP2006 to a non-US-licensed product to address, in part, the requirements under section 351(k)(2)(A) of the PHS Act, the applicant provided data and information to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and established an anaytical-only bridge to the US-licensed reference product; refer to CMC section for details.

The results of study EP06-109 demonstrated PK (Figure 19A) and ANC (Figure 19B) similarity of EP2006 when compared to the US-licensed Neupogen following single 10 mcg/kg SC dose in healthy subjects. The predefined PK similarity limits were met for both $AUC_{0\text{-last}}$ and $C_{max}$ (90% CI, 80-125%). The predefined PD similarity limits were met for both $AUEC_{0\text{-last}}$ and $ANC_{max}$ (95% CI, 80-125%) for ANC. Of note, for ANC, the 90% CI, 80-125% similarity limits were also met (results not shown).

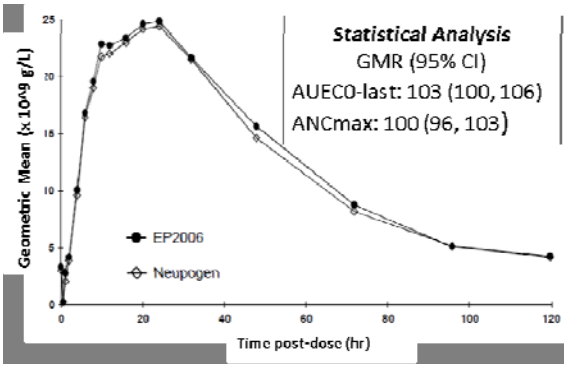
**Figure 19. Time vs. concentration time-profiles and the statistical analysis results for PK (A) and ANC (B) in healthy subjects (EP06-109)**

A. PK profile




GMR, geometric mean ratio

B. ANC profile




GMR, geometric mean ratio

EP2006 showed CD34+ similarity when compared to the EU-approved Neupogen following seven daily SC doses between 2.5, 5, and 10 mcg/kg in healthy subjects. The predefined PD similarity limits were met for CD34+ (95% CI, 80-125%) (Table 10). Of note, the 90% CI, 80-125% similarity limits were also met (results not shown).

**Table 10. Summary of multiple dose CD34+ similarity statistical analysis results from studies using EU-approved Neupogen**

| Study | Dose (mcg/kg) | Statistical Analysis Geometric Mean Ratio (95% CI) | |
|---|---|---|---|
| | | $AUEC_{0-216h}$ | $CD34_{max}$ |
| EP06-103 | 2.5 | 105 (97, 113) | 99 (84, 117) |
| | 5 | 99 (87, 113) | 99 (84, 117) |
| EP06-101 | 10 | 102 (95, 110) | 99 (90, 110) |

Other supportive PK/PD data

EP2006 also showed PK and ANC similarity when compared to the EU-approved Neupogen following single SC doses of 1, 2.5, 5 and 10 mcg/kg in healthy subjects. The predefined PK similarity limits were met for both AUC and $C_{max}$ (90% CI, 80-125%) at all doses, except for $C_{max}$ at the 2.5 mcg/kg dose where the PK similarity was missed marginally (Table 11). The predefined PD similarity limits for AUEC and $ANC_{max}$ were met for ANC (95% CI, 80-125%) (Table 11). Of note, the 90% CI, 80-125% similarity limits for ANC were also met (results not shown).

**Table 11. Summary of single dose PK and ANC similarity statistical analysis results from studies using EU-approved Neupogen**

| Study | Dose (mcg/kg) | PK GMR (90% CI) | ANC GMR (95% CI) |
|---|---|---|---|
| EP06-105 | 1 | $AUC_{0-36h}$: 91 (86, 97)<br>$C_{max}$: 89 (82, 96) | $AUEC_{0-120h}$: 102 (97, 109)<br>ANC $C_{max}$: 100 (94, 105) |
| EP06-103 | 2.5 | $AUC_{0-24h}$: 88 (81, 85)<br>$C_{max}$: 87 (79*, 95) | $AUEC_{0-24h}$: 102 (99, 105)<br>ANC $C_{max}$: 104 (97, 111) |
| | 5 | $AUC_{0-24h}$: 96 (90, 102)<br>$C_{max}$: 96 (89, 104) | $AUEC_{0-24h}$: 101 (98, 103)<br>ANC $C_{max}$: 100 (95, 105) |
| EP06-101 | 10 | $AUC_{0-24h}$: 93 (89, 98)<br>$C_{max}$: 89 (82, 96) | Single dose ANC not reported |

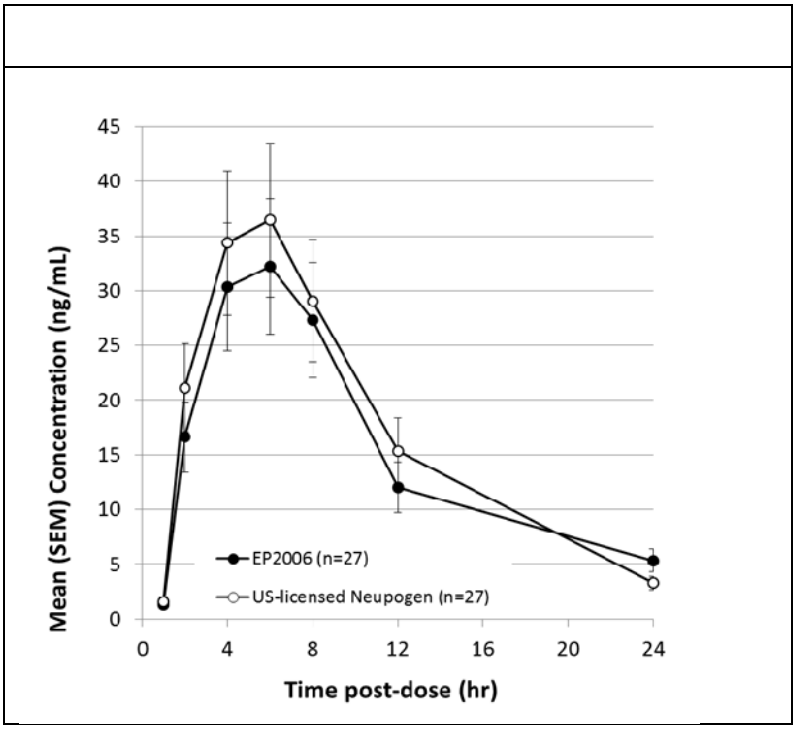
*The lower limit for Cmax at the 2.5 mcg/kg dose fell just outside the 80-125% range.
GMR, geometric mean ratio

**Differences between EP2006 and the Reference Product and Clinical Impact**

As part of the comparative efficacy/safety study EP06-302, the applicant included an exploratory PK sub-study (n=54; 27 per arm) in order to describe the PK of EP2006 and the reference product (US-licensed Neupogen) following a single 5 mcg/kg SC dose in Cycle 1 in patients. EP06-302 was a parallel design study intended to evaluate the efficacy and safety of EP2006 vs. US-licensed Neupogen in patients. The study was not intended to evaluate the PK similarity of EP2006 to US-licensed Neupogen. EP2006 or US-licensed Neupogen was administered daily, starting on Day 2 of each chemotherapy cycle (at least 24 hours after chemotherapy ended) and continued until the ANC recovered to $10 \times 10^{9}$/L after the nadir or up to a maximum of 14 days (which ever occurred first); chemotherapy cycles were three weeks apart.

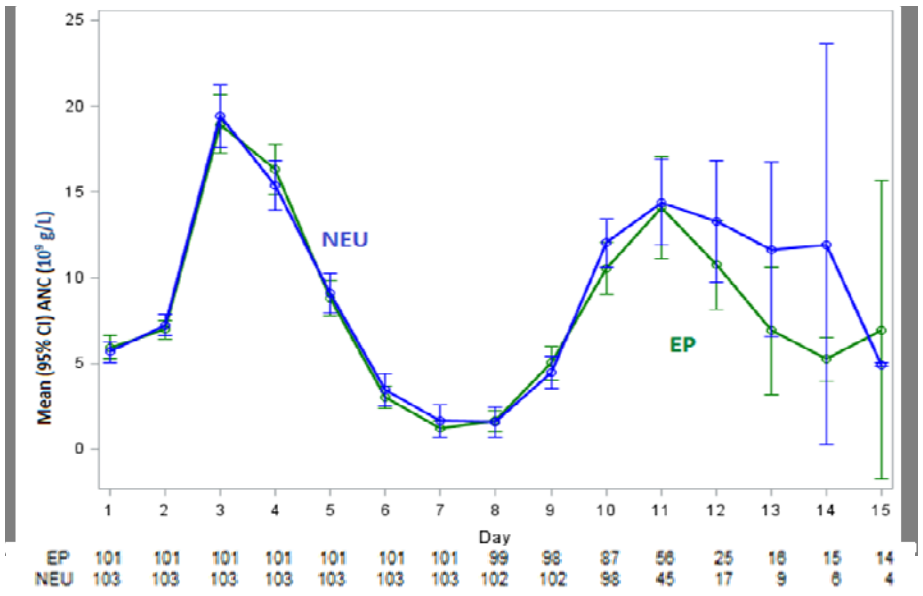
In the exploratory substudy, the exposure (AUC and $C_{max}$) of EP2006 was lower than that observed for US-licensed Neupogen (Figure 20). The inter-subject coefficient of variability (CV%) observed in this sub-study was around 40%, which was greater than that observed in the healthy subject studies (around 20%). The PK sub-study arms were well balanced and comparable to that of the per protocol study arms as it relates to baseline demographics, baseline clinical laboratory values, actual doses administered, and chemotherapy received. Analyzing the stratum of adjuvant versus neoadjuvant chemotherapy did not account for the differences observed in PK either.

**Figure 20. Cycle 1 mean time vs. concentration time-profile in patients (Study EP06-302)**



The differences observed in PK in patients in Cycle 1 did not appear to translate into clinically meaningful PD differences. The time course of the ANC in Cycle 1 is illustrated in Figure 21. The nadir occurred on Days 7 and 8, which is as expected. There were no marked differences in the mean ANC profile between EP2006 and US-licensed Neupogen up to Day 10. However, following Day 10, which is when the ANC had recovered by reaching at least 10 x $10^9$/L in most patients, the number of patients with PD measurements decreased markedly as the ANC recovered in more patients. Of note, per protocol, ANC measurements were only made until the ANC recovered or until Day 15, whichever occurred first. Therefore, the difference in ANC profiles beyond day 10 is likely influenced by low patient numbers. The depth and the time of the ANC nadir in Cycle 1 were also similar in patients receiving EP2006 and patients receiving US-licensed Neupogen. Also, refer to the clinical section below for a description of the overall efficacy and safety results from Study EP06-302.

**Figure 21. Daily mean ANC in Cycle 1 (Study EP06-302).**




The number of subjects in each arm and at each time point is shown at the bottom of the graph.

## Analysis of Similarity

Description of Clinical Uncertainties

The PK and PD study results support a demonstration that there are no clinically meaningful differences between EP2006 and US-licensed Neupogen in terms of safety

and effectiveness. The PK and PD studies conducted in healthy subjects are considered sensitive to detect clinically meaningful differences between products. Single dose PK and ANC similarity margins were met for SC doses between 1-10 mcg/kg. Multiple dose CD34+ similarity margins were met for SC doses between 2.5-10 mcg/kg.

The PK and PD studies have not raised any new uncertainties in the assessment of biosimilarity of EP2006 to US-licensed Neupogen. The comparative clinical study (EP06-302) also supports a demonstration of no clinically meaningful differences between EP2006 and US-licensed Neupogen (see Clinical/Statistics section for details).

# 9 Clinical/Statistics

### Executive Summary

Sandoz submitted two clinical studies that evaluated efficacy and safety endpoints in support of licensure of EP2006. One study (EP06-301) was a non-comparative single arm study in which patients with breast cancer were treated with chemotherapy and then one day later were given daily EP2006 until neutrophil recovery. The other study (EP06-302) was a comparative study that enrolled women with breast cancer undergoing chemotherapy and serves as the main study. The FDA review of the data from Cycle 1 of EP06-302 study supports the Applicant's contention that there are no clinically meaningful differences between EP2006 and US-licensed Neupogen, and confirms the findings made in the FDA analysis of the phase I PK/PD trials (see above).

### Review

Sandoz submitted the results from two clinical studies that evaluated efficacy and safety endpoints: EP06-301 and EP06-302. EP06-301 was a single-arm trial, while EP06-302 was a two arm randomized that was considered to be useful to the evaluation of the biosimilarity of EP2006 (E) to US-licensed Neupogen (N).

EP06-302 was a double-blind parallel group phase 3 study in which women with histologically proven breast cancer who were eligible for neoadjuvant or adjuvant treatment were given six cycles TAC chemotherapy (Taxotere at 75 mg/m$^2$, Adriamycin at 50 mg/m$^2$ and Cytoxan at 500 mg/m$^2$, all given IV on Day 1 of each 21-day cycle) and then randomly assigned to one of the following experimental arms as shown below in Table 12.

**Table 12: Planned Treatment Arms of EP06-302**

| Arm | Number of patients | Cycle 1 | Cycle 2 | Cycle 3 | Cycle 4 | Cycle 5 | Cycle 6 |
|---|---|---|---|---|---|---|---|
| 1 | 48 | E | E | E | E | E | E |
| 2 | 48 | E | N | E | N | E | N |
| 3 | 48 | N | E | N | E | N | E |
| 4 | 48 | N | N | N | N | N | N |
| Abbreviations: E=EP2006; N=US-licensed Neupogen | | | | | | | |

Starting 24 hours after the completion of chemotherapy, N or E was given as a daily subcutaneous injection at a dose of 5 mcg/kg body weight until the ANC recovered to 10 Gi/L after the nadir or up to a maximum of 14 days (which ever occurred first). Subjects in Arms 1 and 2 received EP2006, and those in Arms 3 and 4 received US-licensed Neupogen in Cycle 1 of chemotherapy. The FDA review of efficacy in study EP06-302 focused on a comparison of duration of severe neutropenia in Cycle 1 in patients treated with either EP2006 or US-licensed Neupogen.

**Primary Efficacy Endpoints**

The primary efficacy endpoint was duration of severe neutropenia (DSN) defined as the number of consecutive days in which the patient has an ANC <0.5 Gi/L following Cycle 1 of chemotherapy. The mean number of consecutive days of Grade 4 neutropenia during Cycle 1 was estimated for Arms 1 and 2 (E treatment) and compared with that in Arms 3 and 4 (N treatment). EP06-302 was originally designed as a non-inferiority (NI) study. A one-sided 97.5% confidence internal (CI) for the difference (E-N) in the mean number of consecutive days of Grade 4 neutropenia was derived. EP2006 was considered to be non-inferior to US-licensed Neupogen if the upper bound of this CI lays entirely below the NI margin of +1 day. The primary analysis was analysis of covariance with covariates treatment status (adjuvant vs neoadjuvant) and baseline absolute neutrophil count, based on the per-protocol population (the subgroup of subjects who received treatment and had no major protocol violations).

No similarity margins for equivalence testing were proposed by the sponsor. The data provided in the submission could be used to evaluate the claim that the products are similar by considering the width of the confidence interval for the difference in mean DSN. If the difference is adequately small with a narrow confidence interval, one might conclude that the difference is immaterial.

**Secondary Efficacy Endpoints Included:**

The secondary efficacy endpoints for study EP06-302, which were analyzed with descriptive statistics, included:

a. Incidence of febrile neutropenia (FN) defined as oral temperature ≥38.3 $^{o}$C while having an ANC < 0.5 Gi/L in Cycle 1 and across all cycles

b. Depth of ANC nadir, defined as the patient's lowest ANC in Cycle 1

c. Time to ANC recovery, defined as the time in days from ANC nadir until the patient's ANC increases to ≥ 2 Gi/L after the nadir in Cycle 1.

**Safety Endpoints Included:**

Incidence, occurrence, and severity of (serious) adverse events (AEs/SAEs)

Immunogenicity: Anti-rhG-CSF antibody formation was assessed prior to the first injection of study drug in Cycle 1, on Day 12 of each subsequent cycle, at the end of treatment, and at follow-up visit six weeks after start of the last chemotherapy cycle.

**Analysis of Efficacy Results for Study EP06-302**

The results for the primary endpoint analysis is presented in Table 13 (see below). The 90% CI is (-0.21, 0.28). The analysis showed that EP2006 is equivalent to Neupogen in terms of efficacy as measured by the difference of DSN between N and E being less than 1 day for both the upper and lower bounds of the 90% CI.[22]

**Table 13: Results for the Primary Endpoint for Study EP06-302**

| **Primary Endpoint** | EP2006 (N=101) | Neupogen (N=103) |
|---|---|---|
| Cycle 1<br>Mean DSN (SD) (days) | 1.17 (1.11) | 1.20 (1.02) |
| Neupogen minus EP2006<br>DSN Difference (days)<br>(90%CI) | 0.04<br>(-0.21, 0.28) | |

The results for the Secondary Endpoints for EP06-302 are presented below in Table 14.

22. Roger L. Berger and Jason C. Hsu. Bioequivalence trials. Intersection-union tests and equivalence confidence sets. Statistical Science 11:283-319, 1996.

**Table 14: Results of Secondary Endpoints in Study EP06-302 Cycle 1**

| **Secondary Endpoints** | EP2006 (N=101) | Neupogen (N=103) |
|---|---|---|
| Depth of ANC nadir<br>Mean (SD) ( Gi/L) in Cycle 1 | 0.73 (1.14) | 0.76 (1.31) |
| Time to ANC Recovery<br>Mean (SD) (days) in Cycle 1 | 1.79 (0.97) | 1.68 (0.81) |
| Incidence of FN (%)<br>(Exact 95% CI) in Cycle 1 and across all cycles | 4 (4.0)<br>(1.1, 9.8) | 2 (1.9)<br>(0.0, 5.3) |

The analyses of both the primary endpoint (DSN) as well as secondary endpoints in Cycle 1 of study EP06-302 support the conclusion that there was no clinically meaningful difference with respect to efficacy between EP2006 and Neupogen in Cycle 1.

## Analysis of Safety Results for Study EP06-302

The Safety Analysis Set (SAF) for study EP06-302 included 214 patients distributed into Arms 1-4 as defined in Table 1 above as shown below in Table 15.

**Table 15: Safety Analysis Set for Study EP06-302**

| Arm | Number of Patients | Mean Cumulative Duration of Exposure to Growth Factor Over 6 Cycles (days) |
|---|---|---|
| 1 | 53 | 48.2 |
| 2 | 54 | 47.3 |
| 3 | 55 | 48.3 |
| 4 | 52 | 49.9 |

The baseline demographic features of patients in Arms 1-4 of study EP06-302 are summarized in Table 16 below.

**Table 16: Baseline Demographic and Disease Specific Features in Study EP06-302**

| Parameter | Arm 1<br>N=53 | Arm 2<br>N=54 | Arm 3<br>N=55 | Arm 4<br>N=52 |
|---|---|---|---|---|
| Age (Mean $\pm$ SD) | 51.5 $\pm$ 11.6 | 47.5 $\pm$ 11.64 | 49.7 $\pm$ 11.06 | 46.9 $\pm$ 10.92 |
| Race (White) | 100% | 100% | 100% | 100% |
| BMI (Mean $\pm$ SD) | 26.4 $\pm$ 6.26 | 26.5 $\pm$ 5.52 | 27.7 $\pm$ 4.76 | 27.7 $\pm$ 5.78 |

| Parameter | Arm 1<br>N=53 | Arm 2<br>N=54 | Arm 3<br>N=55 | Arm 4<br>N=52 |
|---|---|---|---|---|
| Mean (Mean ± SD) Time Since Diagnosis (months) | 4.6 ± 23.3 | 1.1 ± 1.1 | 1.3 ± 2.3 | 1.1 ± 1.2 |
| Prior Breast Cancer Surgery | 79.2% | 77.8% | 74.5% | 76.9% |
| Prior Radiation Therapy | 11.3% | 5.6% | 9.1% | 9.6% |
| ECOG PS=0<br>ECOG PS=1 | 71.7%<br>28.3% | 77.8%<br>22.2% | 80.0%<br>20.0% | 75.0%<br>25.0% |

In study EP06-302, 96.3% of the 213 patients experienced at least 1 AE, the majority of which were suspected to be related to chemotherapy with no difference among the Arms. As shown in Table 17 the number of adverse events which were suspected to be due to EP2006 or US-licensed Neupogen products was not different between the various Arms of EP06-302. Only one AE led to study discontinuation which was a patient with blood pressure fluctuation which occurred following US-licensed Neupogen.

**Table 17: Percent Adverse Events on EP06-302 Regardless of Relationship to Treatment (at least 5% in any group)**

| Preferred Term | Arm 1<br>N=53 | Arm 2<br>N=54 | Arm 3<br>N=55 | Arm 4<br>N=52 |
|---|---|---|---|---|
| Alopecia | 77.4 | 81.5 | 78.2 | 82.7 |
| Nausea | 54.7 | 61.1 | 58.2 | 71.2 |
| Asthenia | 37.7 | 51.9 | 58.2 | 53.8 |
| Fatigue | 32.1 | 16.7 | 20.0 | 25.0 |
| Bone Pain | 24.5 | 37.0 | 34.5 | 36.5 |
| Vomiting | 17.0 | 18.5 | 18.2 | 17.3 |
| Pyrexia | 11.3 | 5.6 | 1.8 | 1.9 |
| Diarrhea | 9.4 | 20.4 | 23.6 | 15.4 |
| Musculoskeletal Pain | 9.4 | 1.9 | 3.6 | 1.9 |
| Erythema | 9.4 | 3.7 | 10.9 | 11.5 |
| Leukopenia | 7.5 | 7.4 | 3.6 | 5.8 |
| Abdominal pain | 5.7 | 3.7 | 7.3 | 5.8 |
| Arthralgia | 5.7 | 7.4 | 10.9 | 5.8 |
| Febrile Neutropenia | 5.7 | 9.3 | 1.8 | 1.9 |
| Stomatitis | 5.7 | 5/6 | 0.0 | 3.8 |
| Headache | 5.7 | 5.6 | 3.6 | 1.9 |
| Dizziness | 5.7 | 0.0 | 5.5 | 1.9 |
| Peripheral Sensory Neuropathy | 5.7 | 0.0 | 3.6 | 1.9 |

| Preferred Term | Arm 1 N=53 | Arm 2 N=54 | Arm 3 N=55 | Arm 4 N=52 |
|---|---|---|---|---|
| Abdominal Pain Upper | 3.8 | 0.0 | 9.1 | 3.8 |
| Myalgia | 3.8 | 5.6 | 5.5 | 5.8 |
| Flushing | 1.9 | 5.6 | 0.0 | 3.8 |
| Hypothermia | 0.0 | 5.6 | 1.8 | 1.9 |

A total of 14 SAEs occurred in 12 patients (see Table 18 below). None of these SAEs was considered to be related to EP2006 or US-licensed Neupogen administration. One death occurred due to pulmonary embolism on the sixth day of EP2006 in Cycle 1, and this was not suspected to be due to EP2006.

**Table 18: Percent SAEs in Study EP06-302**

| Primary System Organ Class Preferred Term | Arm 1 N=53 | Arm 2 N=54 | Arm 3 N=55 | Arm 4 N=52 |
|---|---|---|---|---|
| Patients with any SAE | 9.4 | 7.4 | 1.8 | 3.8 |
| Blood and Lymphatic System | 5.7 | 7.4 | 1.8 | 3.8 |
| a. FN | 5.7 | 7.4 | 1.8 | 1.9 |
| b. Anemia | 0.0 | 0.0 | 0.0 | 1.9 |
| c. Leukopenia | 1.9 | 0.0 | 0.0 | 0.0 |
| GI Disorders<br>a. Diarrhea | 0.0 | 0.0 | 0.0 | 1.9 |
| Vascular Disorders | 3.8 | 0.0 | 0.0 | 0.0 |
| a. Embolism | 1.9 | 0.0 | 0.0 | 0.0 |
| b. Hypertensive Crisis | 1.9 | 0.0 | 0.0 | 0.0 |
| Any AE leading to study discontinuation | 1.9 | 0.0 | 1.8 | 0.0 |

**Conclusion**

The results of study EP06-302 did not show evidence of any clinically meaningful differences between EP2006 and Neupogen and confirm the FDA analysis of the phase I PK/PD trials which reached the same conclusion that there are no clinically meaningful differences between EP2006 and US-licensed Neupogen.

# 10 Summary

The conclusion of the comparison of the analytical properties of the clinical product lots of EP2006 and US-licensed Neupogen was that they were highly similar, notwithstanding minor differences in clinically inactive components. The content of the commercial lots of EP2006 was slightly less than that of US-licensed Neupogen, presumably due to dilution of the product at the fill and finish stage of manufacturing. Since none of the commercial lots of EP2006 were used for analytical comparison of the physical or functional properties of EP2006 and US-licensed Neupogen, nor for the PK and PD similarity or clinical studies comparing EP2006 with US-licensed Neupogen, the low content of the commercial lots for EP2006 does not affect the conclusion reached that the clinical lots of EP2006 are highly similar to US-licensed Neupogen.

The results of the PK and PD similarity studies, which were extensive both in terms of the number of the trials, and the doses of EP2006 and Neupogen studied (1.0, 2.5, 5.0 and 10.0 mcg/kg), support the Applicant's contention that there are no clinically meaningful differences in the effectiveness of EP2006 and US-licensed Neupogen for all of the five indications for which US-licensed Neupogen is approved.

This conclusion is also supported by the efficacy results of Cycle 1 of the EP06-302 study which was carried out in patients with breast cancer receiving TAC chemotherapy. The safety analysis of study EP06-302, which is a randomized comparison of EP2006 with US-licensed Neupogen in patients with breast cancer receiving TAC chemotherapy, has not shown any new safety signals.

Taken together in considering the totality of the evidence, the data submitted by the Applicant show that EP2006 is highly similar to US-licensed Neupogen and the clinical data have shown that there are no clinically meaningful differences between EP2006 and US-licensed Neupogen suggesting that EP2006 should receive licensure for each of the 5 indications for which Neupogen is currently licensed. At the time of the completion of this briefing document additional data on the comparative immunogenicity analysis of EP2006 and US-licensed Neupogen are pending and may be forthcoming before the ODAC meeting on January 7, 2015.

# 11 References

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